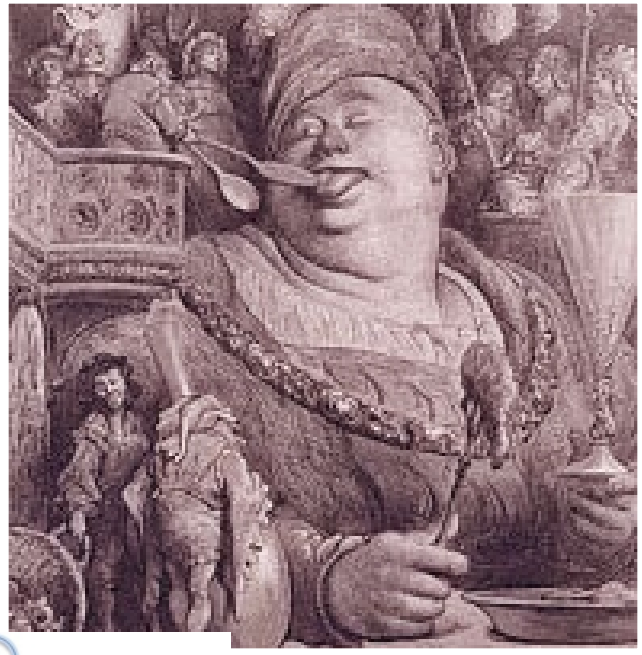
ASSI GULLIVER ASSOCIAZIONE SINDROME DI SOTOS ITALIA

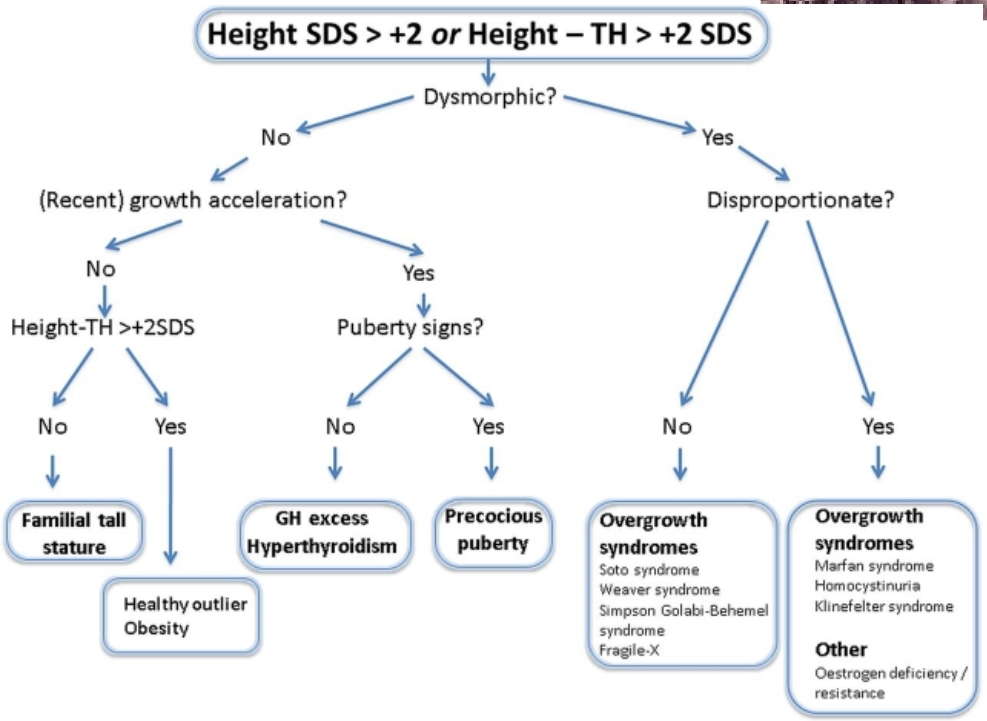
UPDATE SULLA SINDROME DI SOTOS CLINICA E LABORATORIO A CONFRONTO

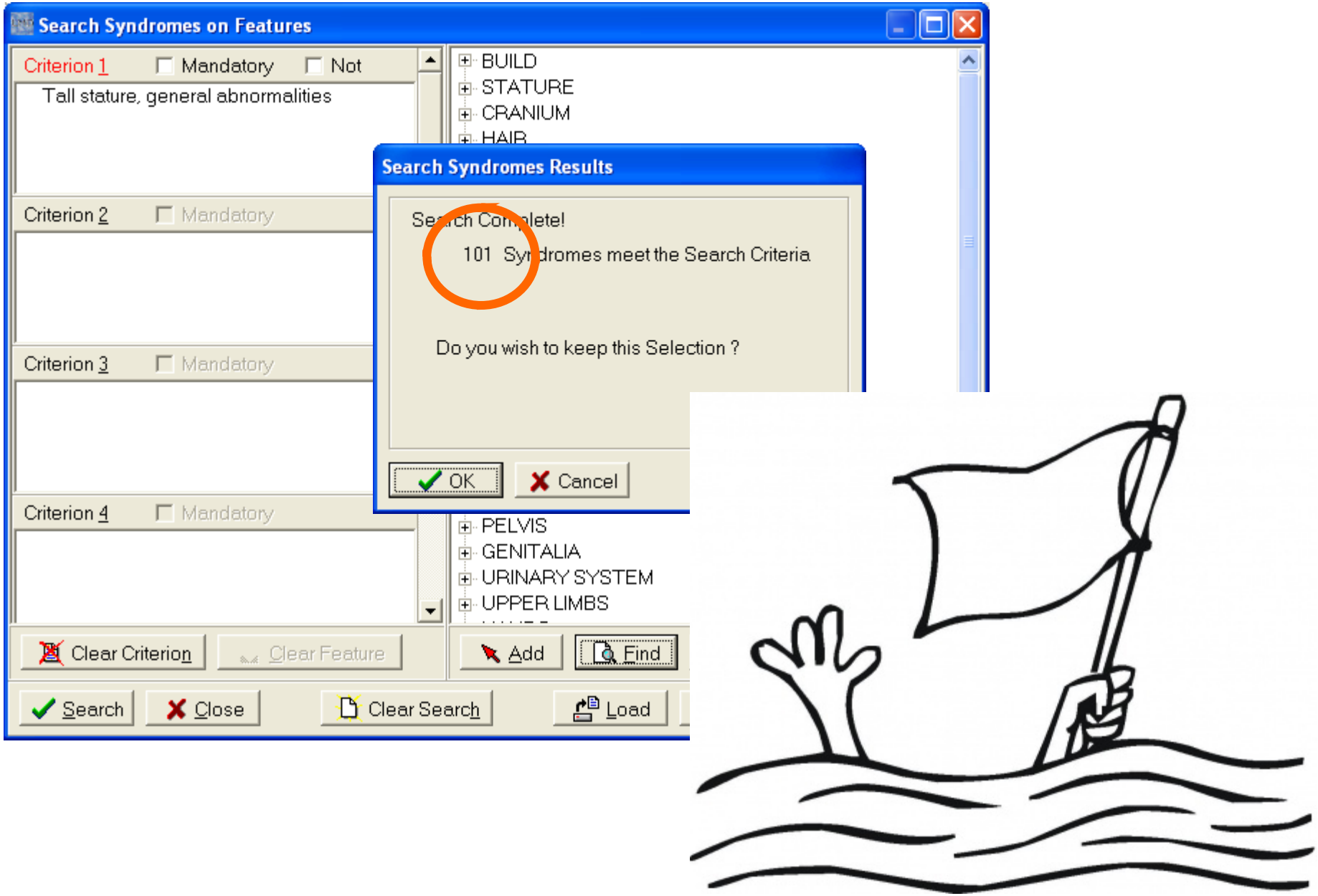
Donatella Milani (Pediatria ad Alta Intensità di cura)

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Il bambino affetto da **MACROSOMIA** è stato storicamente riconosciuto non solo in medicina, ma anche in letteratura; **Francois Rabelais**, nel corso del **sedicesimo secolo**, narrava la storia della nascita di **Gargantua**, un "gigante" che anni dopo avrebbe avuto un figlio, **Pantagruel**, anch'egli affetto da gigantismo.






Search Syndromes on Features
Criterion 1
Mandatory
Not
Tall stature, general abnormalities
Criterion 2
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PELVIS
GENITALIA
URINARY SYSTEM
UPPER LIMBS
Clear Criterion
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Add
Find
Search
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Search Syndromes Results
Search Complete!
101 Syndromes meet the Search Criteria
Do you wish to keep this Selection ?
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OMIM OMIM tall stature Search

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Summary 20 per page Send to:

Search results

Items: 1 to 20 of 168

1. 602472 - CREASES, IN ADVANCED BONE AGE
   OMIM: 602472
   Gene summaries Genetic
2. 236660 - HYDROCEPH SIS
   OMIM: 236660
   Gene summaries Genetic
3. 248350 - MALOCCLUS
   OMIM: 248350
   Gene summaries Genetic tests Medical literature
4. 126950 - DWARFISM WITH **TALL** VERTEBRAE
   OMIM: 126950
   Gene summaries Genetic tests Medical literature
5. #610474 - CAMPTODACTYLY, **TALL STATURE**, AND HEARING LOSS SYNDROME; CATSHLS
   Cytogenetic locations: 4p16.3
   OMIM: 610474
   Gene summaries Genetic tests Medical literature
6. %612578 - **STATURE** QUANTITATIVE TRAIT LOCUS 15; STQTL15
   Cytogenetic locations: 8q21.13
   OMIM: 612578
   Gene summaries Genetic tests Medical literature
7. #613075 - MACS SYNDROME
   Cytogenetic locations: 20p11.23
   OMIM: 613075
   Gene summaries Genetic tests Medical literature
8. 269870 - SHORT **STATURE**-OBESITY SYNDROME; SSOS
   OMIM: 269870
   Gene summaries Genetic tests Medical literature
9. %612579 - **STATURE** QUANTITATIVE TRAIT LOCUS 16; STQTL16

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Genotype-Phenotype Associations in Sotos Syndrome: An Analysis of 266 Individual...

Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individu PubMed

genotype phenotype sotos (31) PubMed

Heterogeneity of NSD1 alterations in 116 patients with Sotos syndrome. PubMed

See more...

Definizioni e classificazione

- **Cohen (1982)**
  - Alta statura familiare
  - Iperaccrescimento prenatale
  - Iperaccrescimento postnatale

- **Beighton (1988)**
  - Iperaccrescimento generalizzato
  - Obesità
  - Iperaccrescimento localizzato
  - Iperaccrescimento digitale

- **Weaver (1994)**
  - Iperaccrescimento generalizzato
  - Iperaccrescimento regionale
  - Iperaccrescimento parametro-specifico

Genetics of obesity and overgrowth syndromes

Best Practice & Research Clinical Endocrinology & Metabolism 25 (2011) 207–220

Identifying genetic causes of weight gain, or tall stature and overgrowth, within this setting can be extremely problematic and yet it is imperative that clinicians remain alert, as identification of a genetic diagnosis has major implications for the individual, family and potential offspring.

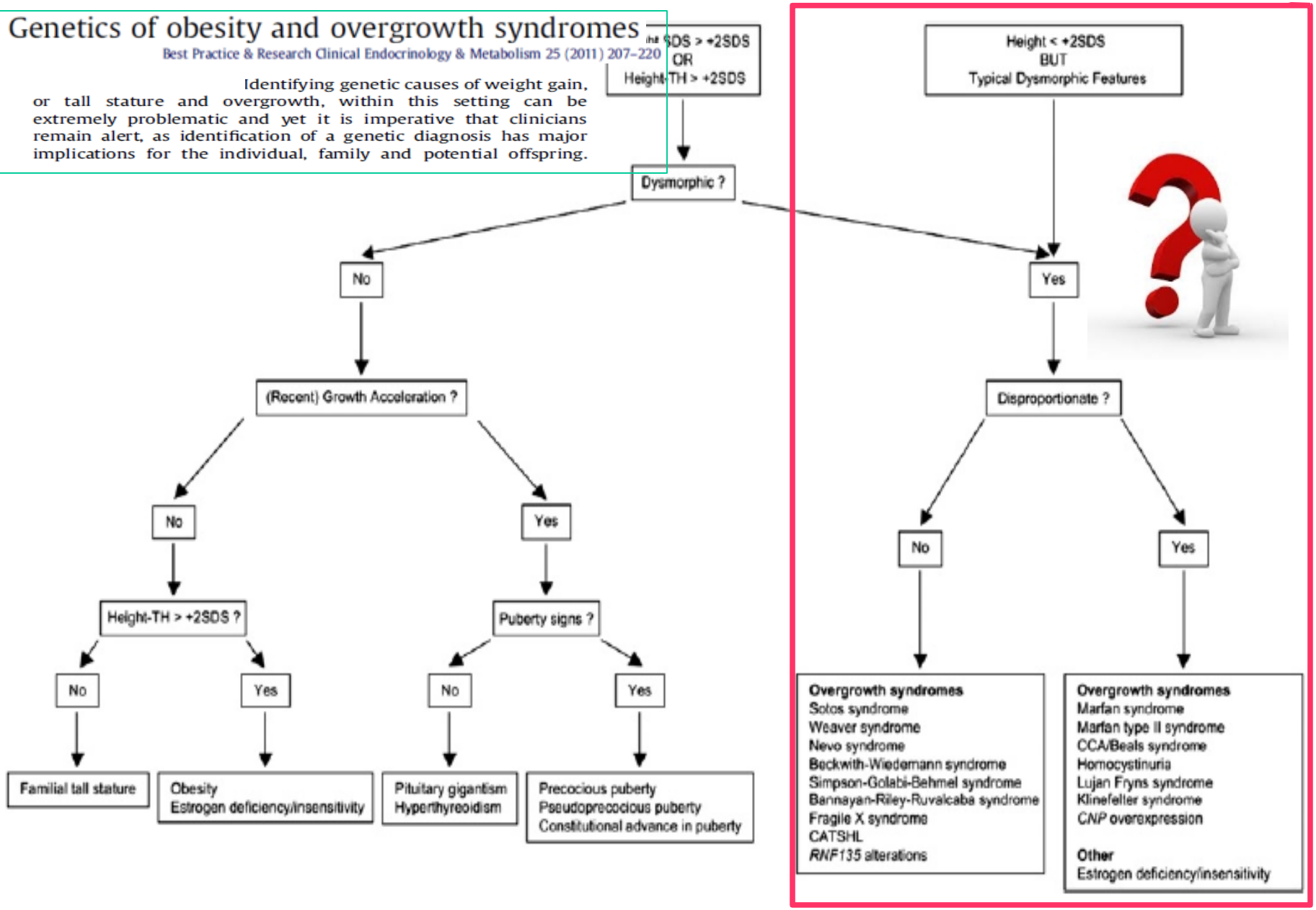


Figure 1. Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes. CCA: Congenital Contractural Arachnodactyly; CNP: C-type natriuretic peptide. Reproduced from Visser et al., Paediatric Endocrinology Reviews 2009.

Schemi superati da…

NOTEVOLE OVERLAP FENOTIPICO

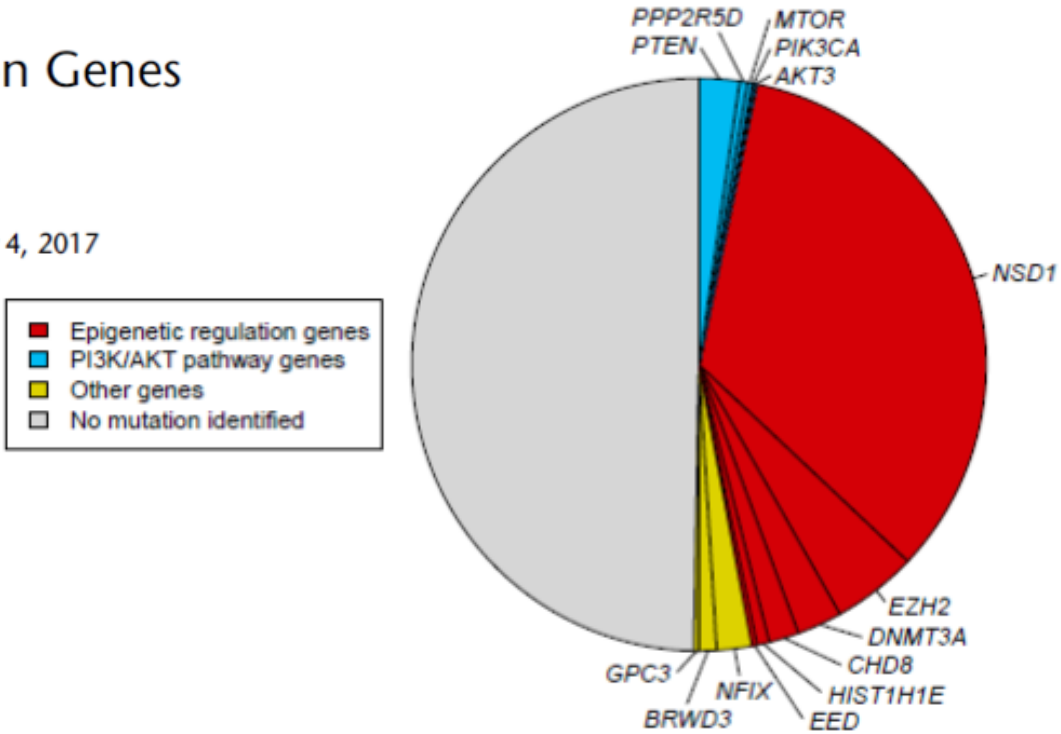
Iperaccrescimento spesso alla nascita
Peso spesso importante quanto l'altezza
Associazione con varie anomalie
Associazione con rischio tumorale
Associazione con ID

NOVITÀ MOLECOLARI

Human overgrowth syndromes are a nebulous group of conditions defined as having height and/or head circumference ≥2 SD above the mean, together with additional phenotypic abnormalities, the most common of which is intellectual disability

Mutations in Epigenetic Regulation Genes Are a Major Cause of Overgrowth with Intellectual Disability

The American Journal of Human Genetics *100*, 725–736, May 4, 2017



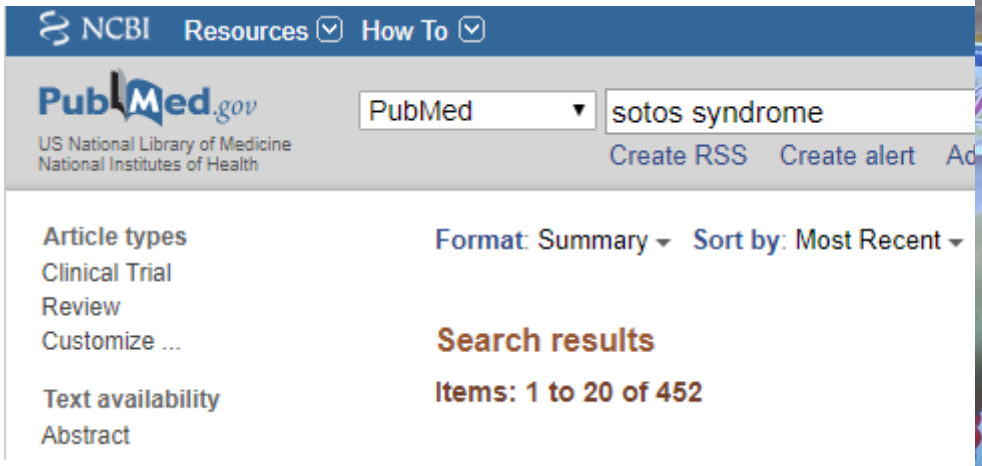
DR 50% (14 geni)

34% SS

Figure 1. Causal Mutation Identified in 50% of OGID Probands
Proportion of pathogenic mutations identified in 710 individuals with OGID. Epigenetic regulation genes (red), including *NSD1* which is the predominant gene, constitute the major gene set. PI3K/AKT pathway genes (blue) also significantly contribute to OGID.

SINDROME DI SOTOS

Incidenza: 1:10-50.000 (1:14000)



1964 SOTOS ET AL.

5 bambini con iperaccrescimento, età ossea aumentata, RPM.

STORIA NATURALE

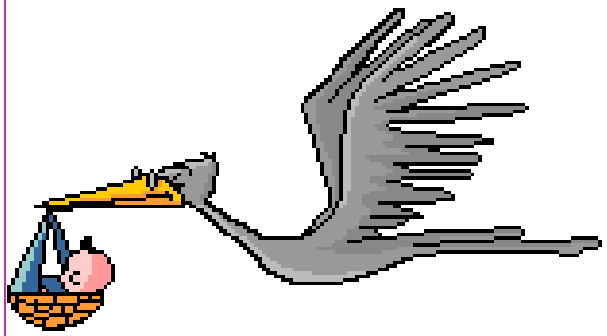
- **GRAVIDANZA**:

  per lo più nella norma (TN); segnalato un aumento di aborti spontanei e morti neonatali in famiglie di pazienti affetti.

- **NASCITA**:

LGA (L +3.2DS, CC +1.8DS, P +1DS); 85% LN >97%; 76-85% dei bambini P<97%. LN maggiore indicatore rispetto a PN

Macrocefalia, ipotonia (90%), problemi respiratori e di alimentazione (40%, rilevanti nel 25%), ipoglicemia, ittero neonatale.



A Case with Neonatal Hyperinsulinemic Hypoglycemia: It is a Characteristic Complication of Sotos Syndrome → Pz deleti

Am J Med Genet Part A 167A:1171–1174.

FENOTIPO NEONATALE: accrescimento

difficoltà suzione
< coordinamento deglutizione
ipotonia
immaturità

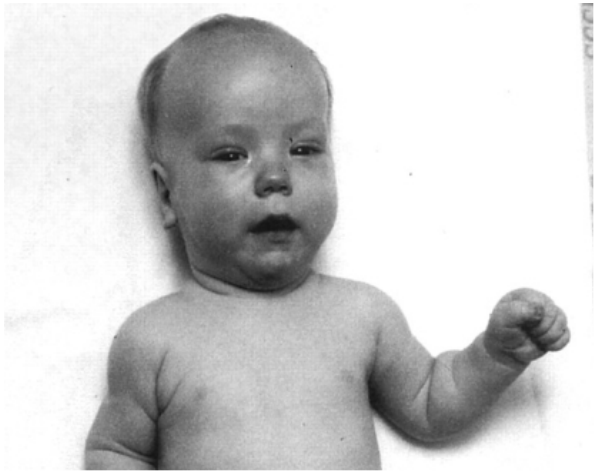
complicanze mediche

difficoltà di alimentazione

problemi nell'accrescimento SP (3-4 mesi)

Se protratto < accrescimento nel primo anno

DIFFICOLTÀ DIAGNOSI

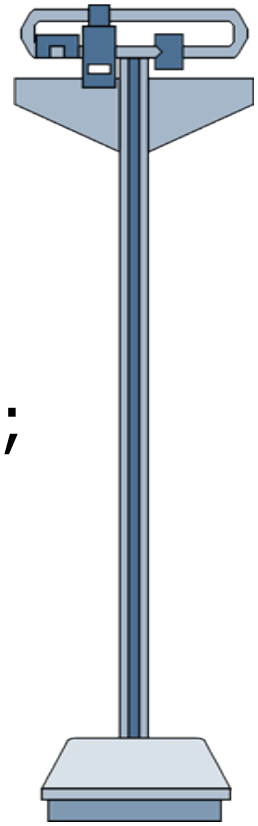


FENOTIPO NEONATALE:

VOLTO:

- macrodolicocefalia
- fronte ampia e prominente
- impianto alto anteriore dei capelli
- costrizione bitemporale (impressione di ipertelorismo)
- palato ogivale
- mento appuntito

FENOTIPO INFANTILE:



ACCRESCIMENTO:

•IPERACCRESCIMENTO evidente i primi 4-5 anni, soprattutto H e CC; poi parallelo alle curve di norma; arti e tronco relativ. sottili, span>altezza

ALTRO:

• iperidrosi, > fame/sete, > soglia dolorifica
•infez. ricorrenti vie aeree/otiti medie (72%), IVU (>20%)
• eruzione dentaria precoce (54%), malocclusione
•piedi piatti, MANI E PIEDI GRANDI
•possibile pubertà precoce (in linea con l'età ossea)

FENOTIPO INFANTILE:

VOLTO:

- macrodolicocefalia
- impianto alto anteriore dei capelli
- fronte prominente
- downslanting palpebrale
- ipertelorismo
- palato ogivale
- mento appuntito

Tendenza a colorazione accentuata di guance, mento e punta nasale, rapide variazioni nel colorito del volto

FENOTIPO ADULTO:

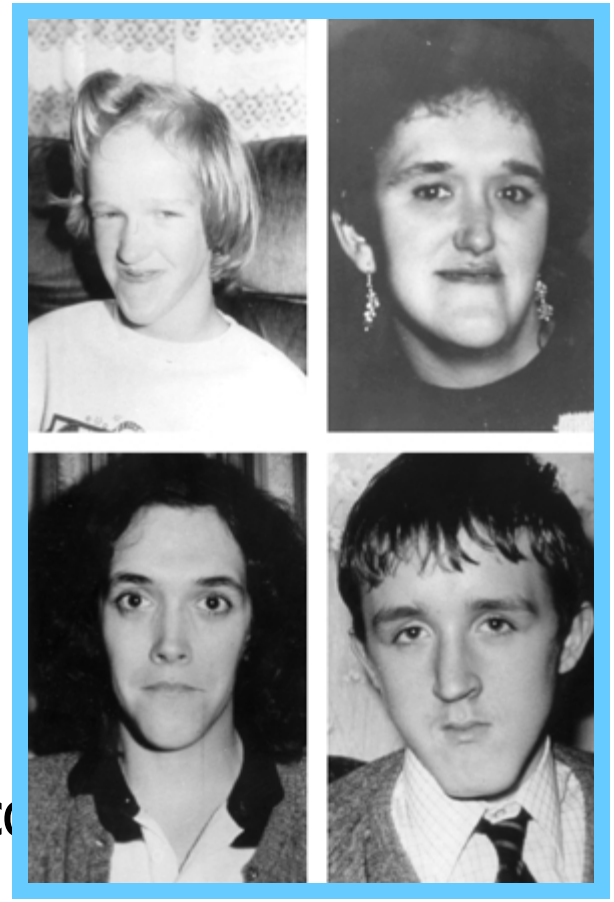
L'ALTEZZA FINALE PUÒ NON ESSERE AUMENTATA (solitamente >50° percentile), in particolare nel sesso femminile

STUDIO INGLESE (AGWU, 1999):
altezza media finale in
18 donne 172.9 cm
(6.2 cm > al target familiare)
9 uomini 184.3 cm
(11.3 cm > al target familiare)

ALTRO: pubertà precoce/oligomenorrea, subfertilità (?)

Macrocefalia

Delezione < mutazione

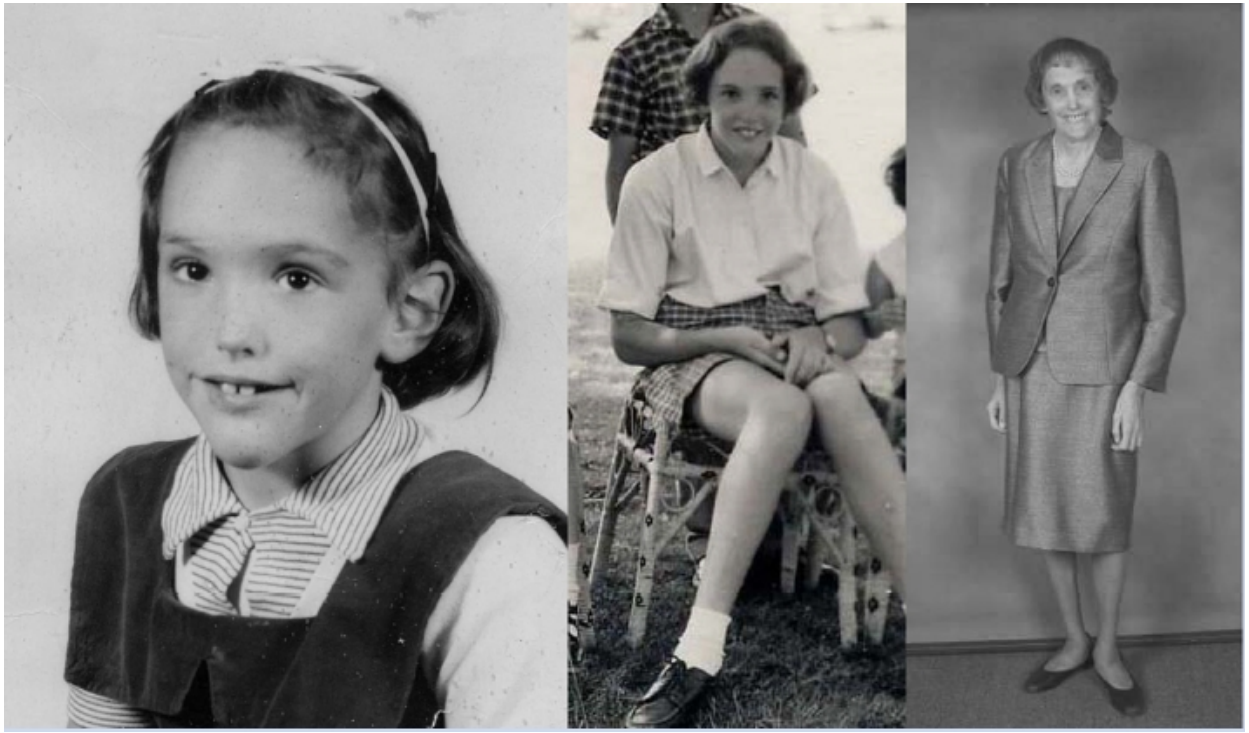


FENOTIPO ADULTO:

- macrocefalia meno evidente
- volto allungato e diametro bizigomatico stretto
- mandibola prominente, squadrata o a punta

Adults With Sotos Syndrome: Review of 21 Adults With Molecularly Confirmed *NSD1* Alterations, Including a Detailed Case Report of the Oldest Person

Am J Med Genet Part A 155:2105–2111.



Altezza media maschi 182 cm, femmine 174 cm

Disturbi psichiatrici 30%, Epilessia 9%

Disturbi visivi 50%

Scoliosi 52%

Tumori 3/27 adulti

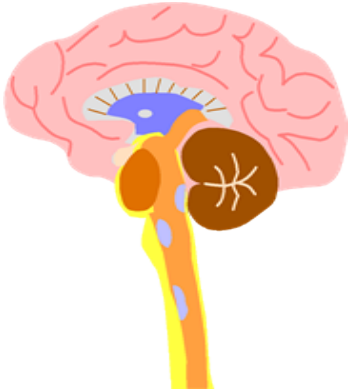
Correlazione genotipo-fenotipo: deleti maggiore difficoltà linguaggio

variazioni SIMILI alla POPOLAZIONE GENERALE, su un BACKGROUND CARATTERISTICO

ACCRESCIMENTO
caratteristicamente molto aumentato fino ai 4-5 anni

GESTALT FACCIALE TIPICA,
CHE EVOLVE E SI MODIFICA NELLE DIVERSE ETA'

SVILUPPO, COMPORTAMENTO, NEUROLOGIA



- **RITARDO MOTORIO E DEL LINGUAGGIO**

impaccio motorio

< coordinazione

spesso deambulazione autonoma > 15 mesi

linguaggio > 2.5 anni

QIV>QIP (opposto ad ASD)

linguaggio recettivo>espressivo

Prob. sottostima QI: bni che frequentano regolarmente la scuola non riconosciuti

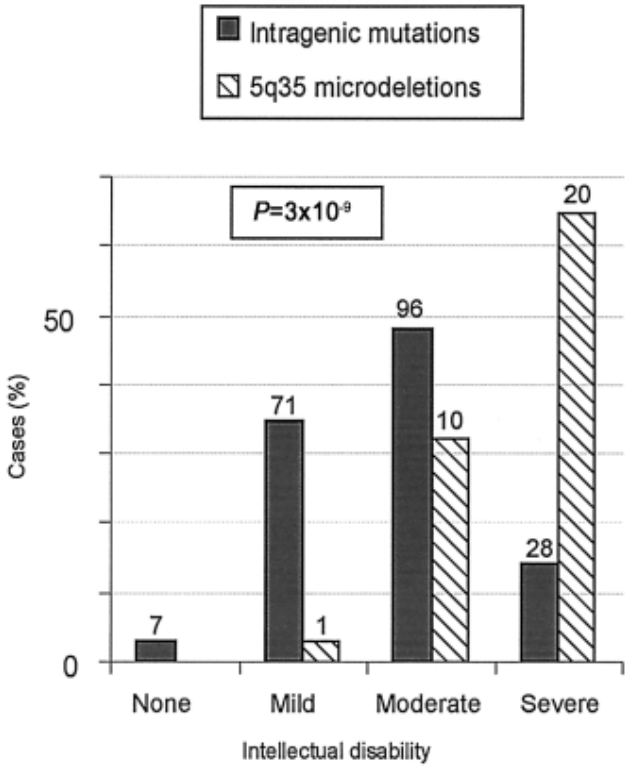
MIGLIORAMENTO CON L'ETÀ

RPM 80-85%, QI 21-129 } Maggioranza N-mild

lieve 30%

moderato 35%

grave 20%



Epilepsia, 53(6):e102–e105, 2012
doi: 10.1111/j.1528-1167.2012.03418.x

BRIEF COMMUNICATION

Seizures and epilepsy in Sotos syndrome: Analysis of 19 Caucasian patients with long-term follow-up

*Francesco Nicita, †Martino Ruggieri, ‡Agata Polizzi, §Laura Mauceri, ¶Vincenzo Salpietro, ¶Silvana Briuglia, *Laura Papetti, *Fabiana Ursitti, **Salvatore Grosso, ††Luigi Tarani, ††Maria Segni, ‡‡Salvatore Savasta, §§Pasquale Parisi, ¶¶Alberto Verrotti, and *Alberto Spalice

*Child Neurology Division, Department of Pediatrics, Policlinico Umberto I, Sapienza University of Rome, Roma, Italy; †Department of Formative Processes, University of Catania, Catania, Italy; ‡National Center for Rare Diseases, Superior Institute of Health, Rome, Italy; §Health Care Center for Obstetrics and Gynecology "Lucina," Catania, Italy; ¶Unit of Genetics and Immunology, Department of Pediatrics, University of Messina, Messina, Italy; **Department of Pediatrics, Gynecology, Obstetrics, and Reproductive Medicine, Pediatric Neurology Section, University of Siena, Siena, Italy; ††Department of Pediatrics, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; ‡‡Department of Pediatrics, University of Pavia, Pavia, Italy; §§Department of Pediatrics, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; and ¶¶Department of Pediatrics, University of Chieti, Chieti, Italy

Summary

Sotos syndrome (SS) is an overgrowth syndrome characterized by typical facial appearance, learning disability, and macrocephaly as cardinal diagnostic features. Febrile (FS) and afebrile seizures are reported in 9–50% of cases. There is no evidence that patients with SS and FS later develop epilepsy, and no studies have investigated the electroclinical features and the long-term outcome in epileptic SS patients. The authors report a series of 19 SS patients with FS and/or epilepsy during childhood and a long-term follow-up. More than half of FS evolved to epilepsy. Temporal lobe seizures were recorded in 40% of patients with SS. Seizures were easy to control with common antiepileptic drugs in almost all patients. A careful neurologic evaluation is useful for SS patients, since seizures are an important finding among people with this overgrowth syndrome.

KEY WORDS: Sotos syndrome, Seizures, Epilepsy, Cerebral gigantism, Overgrowth syndrome.

- **ALTRO**

IPOTONIA (87.5-100%)

SCIALORREA (miglioramento)

DEFICIT DELL'ATTENZIONE

Ansia

AGGRESSIVITÀ nel 50% dei casi con RPM (40-81%). Studio italiano del 2000, non segnalati **CARIOTIPO E FRAX!!!**

Characteristics of Autism Spectrum Disorder in Sotos Syndrome

J Autism Dev Disord (2017) 47:135–143

1% popolazione → 10-20% sindromi

Distinti fenotipi DSA per ogni sindrome!!!

2015 Sheth 68% su 38 pz

2016 Timonen-Soivio 54% su 13 pz

2017 Lane 83% su 78 pz, riduzione nel passaggio all'età adulta

Non differenze di genere

Disturbi inquadrabili nell'ambito di un ampio spettro DSA

The Behavioral Characteristics of Sotos Syndrome

Am J Med Genet Part A 167A:2945–2956.

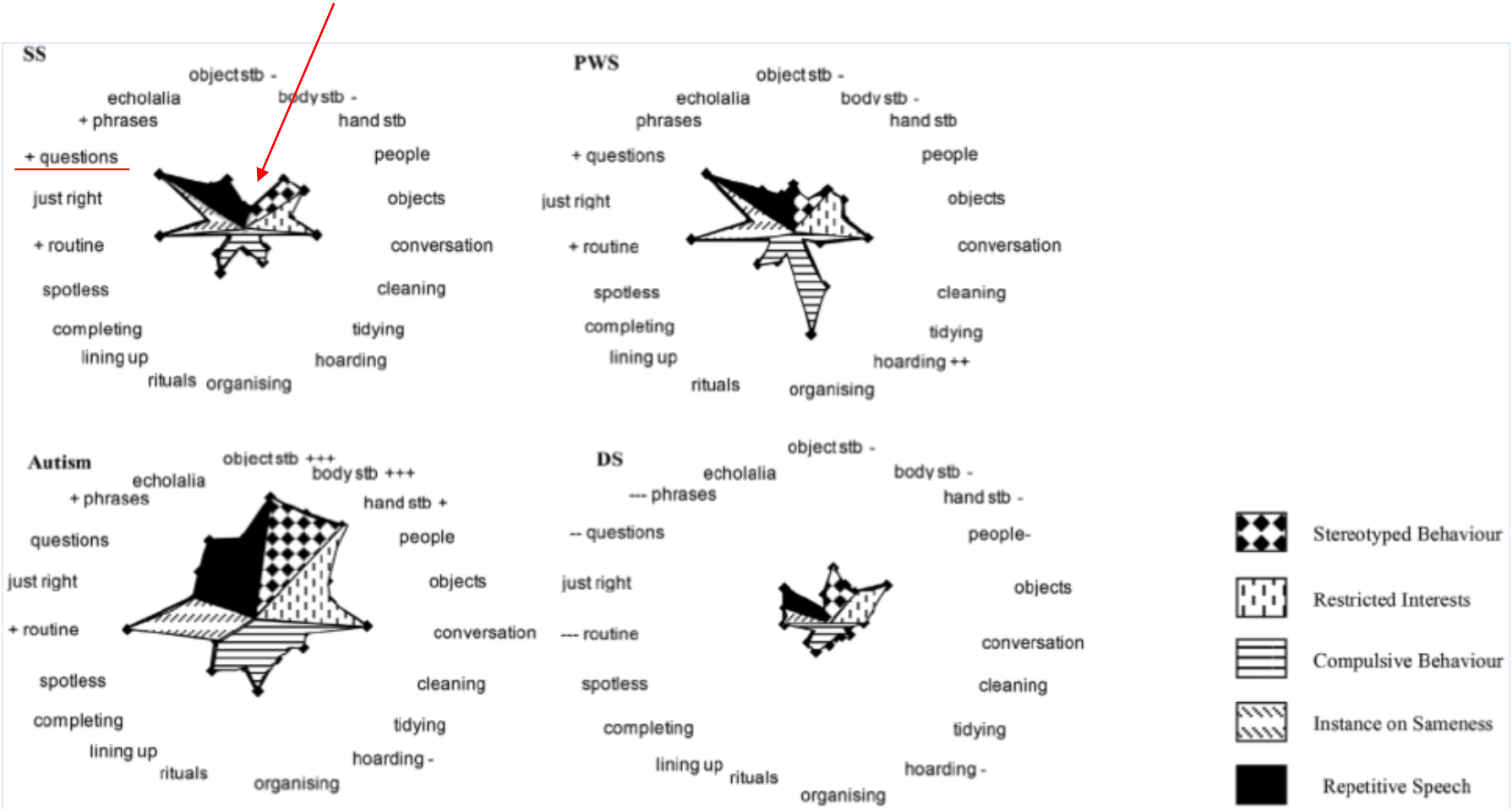
- Atteggiamento autoaggressivo
- Comportamento stereotipato
- Atteggiamenti distruttivi

} 42-43%

- ASD 70.3%, Autismo 32.4%

> ASD rispetto all'atteso ma differenze

maggiore disturbo interazione sociale
minore comportamento ripetitivo
maggiori interessi e passioni


SS
object stb -
echolalia
body stb -
+ phrases
hand stb
+ questions
people
just right
objects
+ routine
conversation
spotless
cleaning
completing
tidying
lining up
hoarding
rituals
organising
PWS
object stb -
echolalia
body stb -
phrases
hand stb
+ questions
people
just right
objects
+ routine
conversation
spotless
cleaning
completing
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hoarding ++
rituals
organising
Autism
object stb +++
echolalia
body stb +++
+ phrases
hand stb +
questions
people
just right
objects
+ routine
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lining up
hoarding -
rituals
organising
Stereotyped Behaviour
Restricted Interests
Compulsive Behaviour
Instance on Sameness
Repetitive Speech

ANOMALIE NEURORADIOLOGICHE

IPOPLASIA DEL CORPO CALLOSO 97.5%
Ventricolomegalia 63%

Utilizzabili per la **DIAGNOSI DIFFERENZIALE** secondo gli autori del principale studio

CAUTELA

- PRESENTI ANCHE IN ALTRE SINDROMI DA IPERACCRESCIMENTO
- UTILE AGGIUNTA AI PRINCIPALI CRITERI
- UTILITA' RMN ENCEFALO IN SS…

ASPETTI RADIOLOGICI

RX CARPO: ETÀ OSSEA AUMENTATA (71%)

Falangi distali corte rispetto a metacarpi e falangi prossimali

ASPETTI ORTOPEDICI

Alterazioni dei piedi (in particolare PIEDE PIATTO) (50%)

SCOLIOSI → Diversa da scoliosi idiopatica infantile (epoca precoce, progressione rapida fino ai 4 anni…)

iperlassità articolare
piede piatto
} Connettivo >15%

MANIFESTAZIONI OCULARI

POCO DOCUMENTATE, MA FREQUENTI: 50% secondo uno studio del 1994.

Più comuni:

DISTURBI RIFRATTIVI

STRABISMO (40%)

ALTRI:

Megalocornea, ipoplasia dell'iride, cataratta, megaloftalmo, nistagmo, pallore del disco ottico, distrofia/atrofia retinica, glaucoma, displasia setto-ottica

Craniofacial and Oral Features of Sotos Syndrome: Differences in Patients With Submicroscopic Deletion and Mutation of *NSD1* Gene

Am J Med Genet Part A 155:2933–2939.

Su 8 pazienti, 5 deleti e 3 mutati, 2011

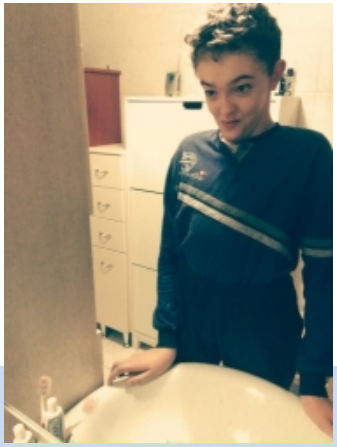


TABLE II. Oral and Dental Anomalies in Eight Patients

	Deletion type patients					Mutation type patients			Total	
Oral anomalies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Deletion type**	**Mutation type**
High palate	+	+	+	+	+	+	+	+	5/5	3/3
Excessive tooth wear	+	+	+	+	+	+	+	+	5/5	3/3
Hypodontia	−	+	+	+	+	+	+	+	4/5	3/3
Maxillary recession	+	−	+	+	+	+	+	−	4/5	2/3
Mandibular recession	−	−	+	+	+	−	+	−	3/5	1/3
Malocclusion										
Scissors bite	+	−	+	+	−	−	−	−	3/5	0/3
Cross bite	−	+	−	−	+	−	−	−	2/5	0/3
Deep bite	+	−	+	+	+	+	+	+	4/5	3/3
Crowding	+	+	+	+	+	+	+	+	5/5	3/3
Small dental arch	+	+	+	+	+	−	+	−	5/5	1/3
Maxilla	N	N	N	N	N	U	U	U		
Mandibula	S	U	S	S	U	U	U	U		
Labioclination of maxillary central incisor	+	+	+	+	+	−	−	−	5/5	0/3
Enamel hypoplasia	−	+	+	−	−	−	−	−	2/5	0/3
Ectopic tooth eruption	−	−	−	+	−	+	−	−	1/5	1/3

N, narrow dental arch; U, U-shaped dental arch; S, saddle-shaped dental arch; +, present; −, absent.

2009, 69% di 13 pz

Delezione > malocclusione

Proposta panoramica a 7 anni

CARDIOPATIE CONGENITE

DIA,
DIV,
PDA

INCIDENZA

50% (Kaneko et al, 1987)

12.5% (Cole and Hughes, 1994)

35% (Naritomi et al, 1997)

8% (Noreau et al, 1998)

41% (Tsukahara et al, 1999)

X10 rispetto alla popolazione generale

= studi giapponesi

= studi europei-americani

Anomalie renali

Poco segnalate, 15%, soprattutto RVU

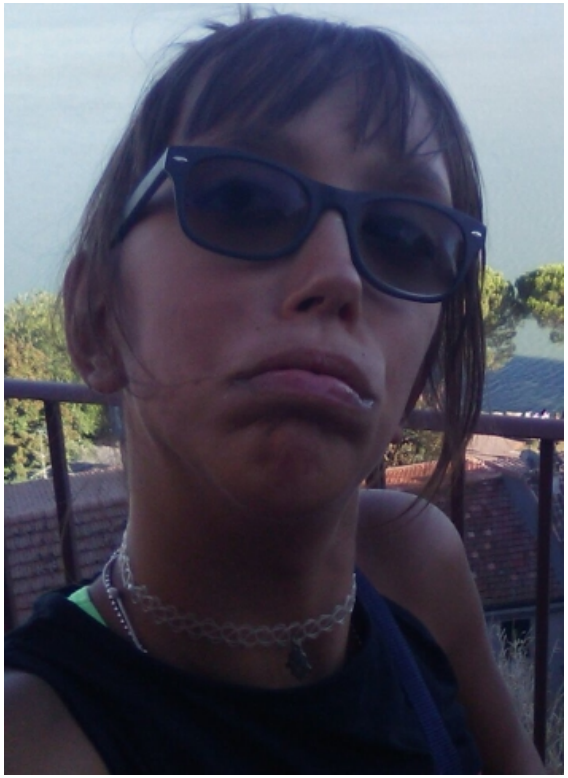
Nefrocalcinosi in 5 pz con delezione (2007, 2011)
Ipercalcemia in 2 pz con delezione (2011, 2014)

Ipotizzato ruolo FGFR4

Attenzione a double trouble: IRC in SS ma mutazione ADPKD!!!

Aspetti endocrinologici/ginecologici

- Ipoglicemia iperinsulinemica
- Ipotiroidismo
- Ipoparatiroidismo 1 caso (2015)
- Fibromatosi ovarica 2 casi
- Possibile pubertà precoce



PREDISPOSIZIONE ALLO SVILUPPO DI TUMORI

Inclusi tumori benigni

Descritti a volte in condizioni Sotos-like

INCIDENZA

3.9-7% (Cohen, 1989; Wit et al, 1985; Gorlin, 1990)

2.2% (Hersh et al, 1992)

- **VARIE SEDI CORPOREE**
- **VARI TIPI DI NEOPLASIE**
- **VARIE ETA'**

tumore di Wilms
epatoblastoma
neuroblastoma
tumore misto della parotide
tumori neuroectodermici
carcinoma epidermoide vaginale
LLA
linfoma non Hodgkin
fibromi ovarici bilaterali calcificati/ossificati
granuloma a cellule giganti della mandibola

emangiomi multipli
carcinoma polmonare a piccole cellule
tumore testicolare
osteocondroma
teratoma sacrococcigeo
fibroma cardiaco VSX
carcinoma gastrico

Correlazione soprattutto con:
TUMORI SOLIDI ECTODERMICI
E
MESODERMICI

Negli ultimi 2 anni segnalazione solo di un astrocitoma in pz adulto

Recommendations for Cancer Surveillance in Individuals with RASopathies and Other Rare Genetic Conditions with Increased Cancer Risk

Clin Cancer Res; 23(12); e83–e90. ©2017 AACR.

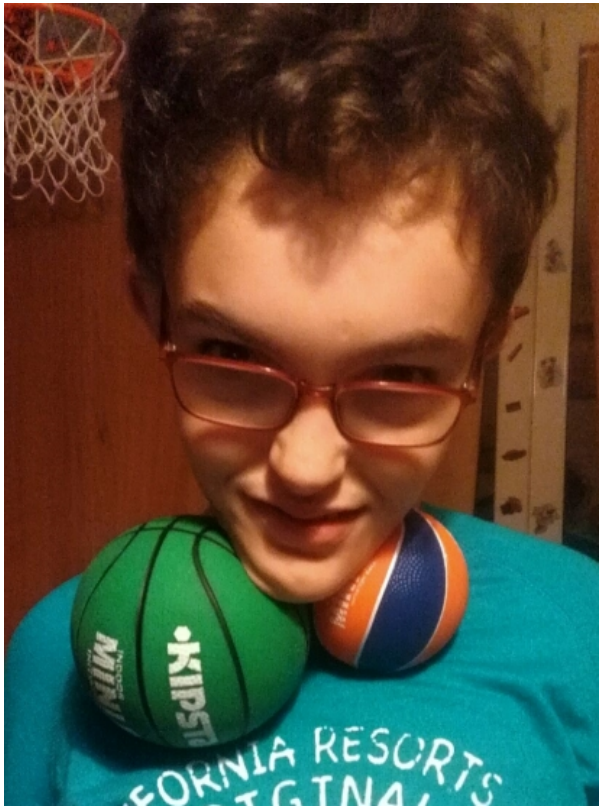
Table 1. Summary of cancer surveillance recommendations

Syndrome	Childhood cancer risk	Surveillance guidelines
I. Surveillance warranted		
Costello syndrome	15% by 20 yrs: ERMS, NBL, bladder cancer	0 to 8–10 yrs: physical exam and AP US ± CXR q 3–4 mths From 10 yrs: annual urinalysis
NS—specific *PTPN11* or *KRAS* mutations	High risk of myeloproliferative disorder/JMML	0 to 5 yrs: physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
CBL syndrome	High but not precisely defined JMML risk; more rarely other neoplasms	0 to 5 yrs: Physical exam (with assessment of spleen) and CBC with differential q 3–6 mths
SGS—mild	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider periodic AP US, AFP/βHCG
II. Baseline only		
SGS—severe	Unknown but may approximate 10–15%: SC-GCT and PNET, HBL	Attention for congenital tumors on baseline imaging for SGS Consider addition of AFP/βHCG to baseline bloodwork for SGS
III. No surveillance		
For all of the following:	<5% or unknown but low likelihood	No routine surveillance Increased awareness and low threshold for investigating new potential tumor-related symptoms
NS (non-high risk mutations)	Dysembryoplastic neuroepithelial tumors, ALL, NBL, RMS, others	
NSLAH	e.g., NBL, myelofibrosis	
NSML	e.g., acute leukemias	
CFCS	e.g., ALL, NHL	
Legius syndrome	Few cancers reported to date	
Sotos syndrome	e.g., NBL, ALL, AML, HBL, SCT, etc.	
Weaver syndrome	e.g., NBL, hematologic malignancies	
Rubinstein–Taybi syndrome	e.g., HBL, NBL, RMS, CNS tumors, carcinomas, etc.	
NKX2-1 syndrome	No evidence for cancer predisposition	

Aspetti infettivologici/ORL

Am J Med Genet Part A 173A:1090–1093.

- Infezioni respiratorie ricorrenti/otiti medie ricorrenti, ipoacusia trasmissiva [Baujat and Cormier-Daire, 2007].
- Apnea ostruttiva nel sonno
- SNHL in alcuni casi



no protocollo screening

Approfondiamo?

Prof.ssa P.Marchisio, Dr.ssa Elena Baggi

- ✓Visita infettivologia respiratoria
- ✓Impedenzometria
- ✓Polisonnografia

Vaccination coverage of children with rare genetic diseases and attitudes of their parents toward vaccines

Susanna Esposito, Marta Cerutti, Donatella Milani, Francesca Menni, and Nicola Principi

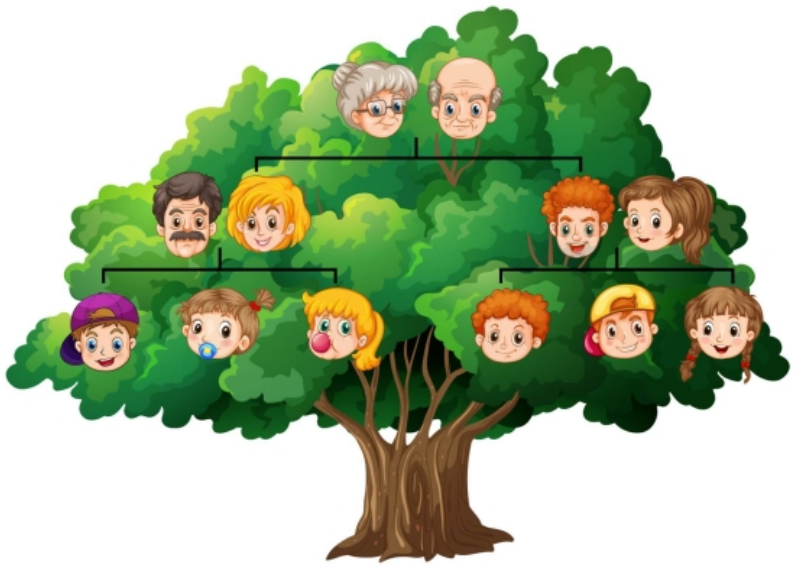
HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 3, 801–805

enrolled. The coverage of all the recommended vaccines in children with genetic syndromes was significantly lower than that observed in healthy controls ($p < 0.05$ for all the comparisons). However, when vaccinated, all of the patients, independent of the genetic syndrome from which they suffer, were administered the primary series and the booster doses at a similar time to healthy controls. In comparison with parents of healthy controls, parents of children with genetic diseases were found to more frequently have negative attitudes toward vaccination ($p < 0.05$ for all the comparisons), mainly for fear of the emergence of adverse events or deterioration of the underlying disease. This study shows that vaccination coverage is poor in pediatric patients with RSTS, BWS, and SS and significantly lower than that observed in healthy children. These results highlight the need for educational programs rents and pediatricians to increase immunization coverage in childre ses.

Attitude	Rubinstein-Taybi syndrome (n = 15)	Sotos syndrome (n = 14)	Beckwith-Wiedemann syndrome (n = 28)	Healthy controls (n = 57)
Position toward vaccines, n. (%)				
Favorable	8 (53.3)[1]	6 (42.8)[1]	18 (64.3)[1]	50 (87.7)
Against	6 (40.0)[1]	8 (57.2)[1]	9 (32.1)[1]	2 (3.5)
Neither favorable nor against	1 (6.7)	0 (0.0)	2 (7.1)	5 (8.8)
Reasons for being against vaccines, n. (%)				
Doubts on efficacy	0/6 (0.0)	1/8 (12.5)	1/9 (11.2)	0/2 (0.0)
Worsening of the underlying disease	2/6 (33.3)	3/8 (37.5)	4/9 (44.4)	0/2 (0.0)
Doubts and/or fear of adverse events	3/6 (50.0)	3/8 (37.5)	4/9 (44.4)	1/2 (50.0)
To prefer the disease instead of its prevention	1/6 (16.7)	1/8 (12.5)	0/9 (0.0)	1/2 (50.0)
Why do you vaccinate your child? n. (%)				
It is mandatory	7 (46.7)	8 (57.1)	9 (32.1)	4 (7.0)
Hospital pediatrician recommends to vaccinate	2 (13.3)	0 (0.0)	5 (17.9)	0 (0.0)
Primary care pediatricians recommend to vaccinate	5 (33.3)[1]	6 (42.9)[1]	11 (39.3)[1]	50 (87.7)
It is recommended by TV/newspapers/internet	1 (6.7)	0 (0.0)	3 (10.7)	3 (5.3)
Who recommends vaccinating your child? n. (%)				
Ministry of health	1 (6.7)	4 (35.7)	6 (21.4)	4 (7.0)
Primary care pediatrician	6 (40.0)[1]	5 (50.0)[1]	12 (42.9)[1]	52 (91.2)
Hospital pediatrician	8 (53.3)[1]	4 (28.6)[1]	7 (25.0)[1]	0 (0.0)
Other (Regions, other parents, friends)	0 (0.0)	1 (7.1)	3 (10.7)	1 (1.8)
Are you in favor of influenza vaccination? n. (%)				
Yes	3 (20.0)	4 (28.6)	2 (7.1)	20 (35.1)
No	12 (80.0)	10 (71.4)	26 (92.9)	37 (64.9)
If no, why?				
My child has no major complications	7/12 (58.3)	2/10 (20.0)	13/26 (46.4)	24/37 (64.9)
Influenza vaccine is not effective	2/12 (16.7)	4/10 (40.0)	1/26 (3.6)	1/37 (2.7)
I have fear of adverse event	4/12 (33.3)	4/10 (40.0)	10/26 (35.7)	9/37 (24.3)
No pediatrician has recommended it	2/12 (16.7)	0/10 (0.0)	4/26 (14.3)	3/37 (8.1)

Consulenza genetica

- Sporadica
- AD, espressività variabile
- Mosaico
  - Saugier-Veber 2007
  - Castronovo 2013



Somatic-Gonadal Mosaicism Causing Sotos Syndrome

Am J Med Genet Part A 170A:3360–3362.

Diagnosi prenatale

- Overlap
- Screening su sangue materno per trisomie talora +
- Macrosomia evidente dopo la 20° sg
- Macrocefalia aspecifica
- Poliidramnios
- Possibile solo mediante tecniche genetiche (su sospetto specifico per mutazioni, anche generico per delezioni)

Prenatal diagnosis of Sotos syndrome characterized by fetal growth restriction

Sotos Syndrome: Antenatal Presentation

American Journal of Medical Genetics Part A 146A:1312–1313 (2008)

Facciamo il punto

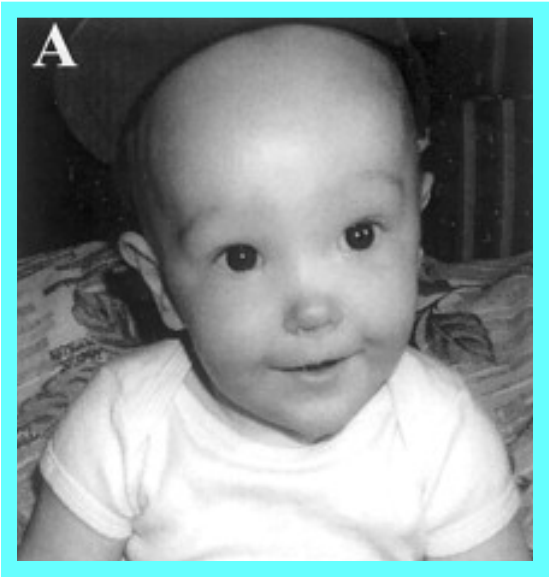
diagnosi

CLINICA
MOLECOLARE

Assistenza

UTILITA' INDIVIDUO
UTILITA' POPOLAZIONE AFFETTI

DIAGNOSI



La diagnosi di SS è basata principalmente sulla presenza di ***DISMORFISMI SPECIFICI*** in un bambino con ***IPERACCRESCIMENTO.***

Molte caratteristiche sono poco accentuate o comuni => rischio di diagnosi scorretta (FP/FN)

CRITERI DIAGNOSTICI

- **IPERACCRESCIMENTO**
- **ETÀ OSSEA AUMENTATA**
- **RPM**
- **DISMORFISMI**

  (specifico, soggettivo)

- soglia di normalità
- diverse sindromi

ETÀ MEDIA ALLA DIAGNOSI: 26.6 mesi nel 1994; non eseguiti ulteriori studi in tal senso, è probabile che l'età media alla diagnosi si sia ridotta e la frequenza di diagnosi sia aumentata

Quando i **CRITERI** sono strettamente applicati durante l'**INFANZIA**, tutti e quattro sono presenti nel **75%** dei casi di **S.Sotos**, ed in **< 20%** di **altri pattern di iperaccrescimento** specifici e non specifici (Wit 1985, Cole, 1994)

criteri di Cole e Hughes

pazienti con mutazioni

4 criteri	30%
3 criteri	39%
2 criteri	31%

SOTTOSTIMA

Cardinal features (present in ≥90% of persons with Sotos syndrome)

- Characteristic facial appearance
- Learning disability
- Overgrowth

Major features (present in 15%-89% of persons with Sotos syndrome)

- Behavioral problems
- Advanced bone age
- Cardiac anomalies
- Cranial MRI/CT abnormalities
- Joint hyperlaxity/*pes planus*
- Maternal preeclampsia
- Neonatal complications
- Renal anomalies
- Scoliosis
- Seizures

Attualmente...

Come ci aiuta la genetica?

Correlazione genotipo-fenotipo: MICRODEL/MUT PUNTIFORMI
Migliore definizione criteri clinici diagnostici (iperaccrescimento, DIA, età ossea, corpo calloso…)

TABLE 3. Clinical Manifestations in Patients With *NSD1* Alterations

Clinical features	Total *NSD1* intragenic mutations	Truncating mutations[a]	Missense mutations or in-frame deletions	Common large 5q35 deletions	*NSD1* total deletion[b]
Number of patients	89	70	19	10	1
Growth					
Birth OFC >90th percentile	49/74 (66%)	40/60 (67%)	9/16 (56%)	4/10 (40%)	na
Birth length >95th percentile	51/77 (66%)	43/63 (68%)	8/15 (53%)	2/10 (20%)	na
Postnatal OFC≤ +2 SD	14/80 (17.5%)	7/65 (11%)	8/17 (47%)	3/8 (37.5%)	0/1
Postnatal OFC≥ +6 SD	7/84 (8%)	7/69 (10%)	1/16 (0%)	0/8 (0%)	1/1
Height≥+4 SD	32/86 (37%)	27/71 (38%)	5/16 (31%)	2/9 (22%)	1/1
Cognitive development					
Normal intelligence	11/68 (16%)	9/58 (15.5 %)	3/9 (33%)	0/10 (0%)	1/1
Severe mental retardation	2/69 (3%)	2/59 (3%)	0/11 (0%)	3/9 (33%)	0/1
Able to walk (in months)	19.5 (10–60)	19.9 (10–60)	17.6 (13–24)	28 (18–60)[c]	30
Able to read (>7 years)	22/32 (69%)	18/26 (69%)	4/6 (67%)	0/4 (0%)	1/1
Epilepsy					
Epilepsy	12/79 (15%)	12/61 (20%)	0/18 (0%)	2/9 (22%)	0/1
Including benign West	3	3	0	0	0
Febrile convulsions	10/83 (12%)	7/65 (11%)	3/19 (27%)	0/9 (0%)	
Malformations					
Cardiac malformation	6/76 (8%)	6/60 (10%)	0/17 (0%)	3/8 (37.5%)	1/1
Renal malformation	9/73 (12%)	9/56 (16%)	0/17 (0%)	4/8 (50%)	0/1
Ocular malformation	0/79	0/63	0/17	1/10	0/1
Cleft palate	2/79	2/63	0/17	0/10	0/1
Meckel's diverticulum	1/76	1/60	0/17	0/10	0/1
Athyreosis	1/76	1/60	0/17	0/10	0/1
Nephrocalcinosis	0/73	0/56	0/17	1/8	0/1
Tumor	1/80	1/63	0/18	0/10	0/1

[a]Including nonsense mutations, frameshift mutations, splice mutations, exonic deletions, or duplication, except the mosaic deletion of exons 18 and 19.
[b]Patient 1 on Figure 2.
[c]One patient was still unable to walk at 11 years of age.
na, not available.

Delezioni vs mutazioni puntiformi

This study confirms that the phenotype in patients with large 5q35 deletions is more severe than in patients with *NSD1* mutations. Moreover, we have evidence for milder phenotype (psychomotor and cognitive impairment, OFC, frequency of malformations, and epilepsy) in patients with missense mutations vs. patients with truncating mutations. However, the high clinical variability observed in Sotos syndrome, even in patients with the same mutation, demonstrates that other factors, genetic, epigenetic, or environmental, play important roles in the severity of the phenotype. This study confirms the heterogeneity of *NSD1* alterations in Sotos syndrome and, therefore, the need to complete sequencing analysis by the screening for partial deletions and duplications to ensure an accurate molecular diagnosis of this syndrome.

Mutazioni missenso vs troncanti

Attenzione ai quadri LIKE

BWS

SGBS

S.Malan

WS

DNMT3A

SETD2

FRAX

PTEN

Expansion of the phenotype of Kosaki overgrowth syndrome

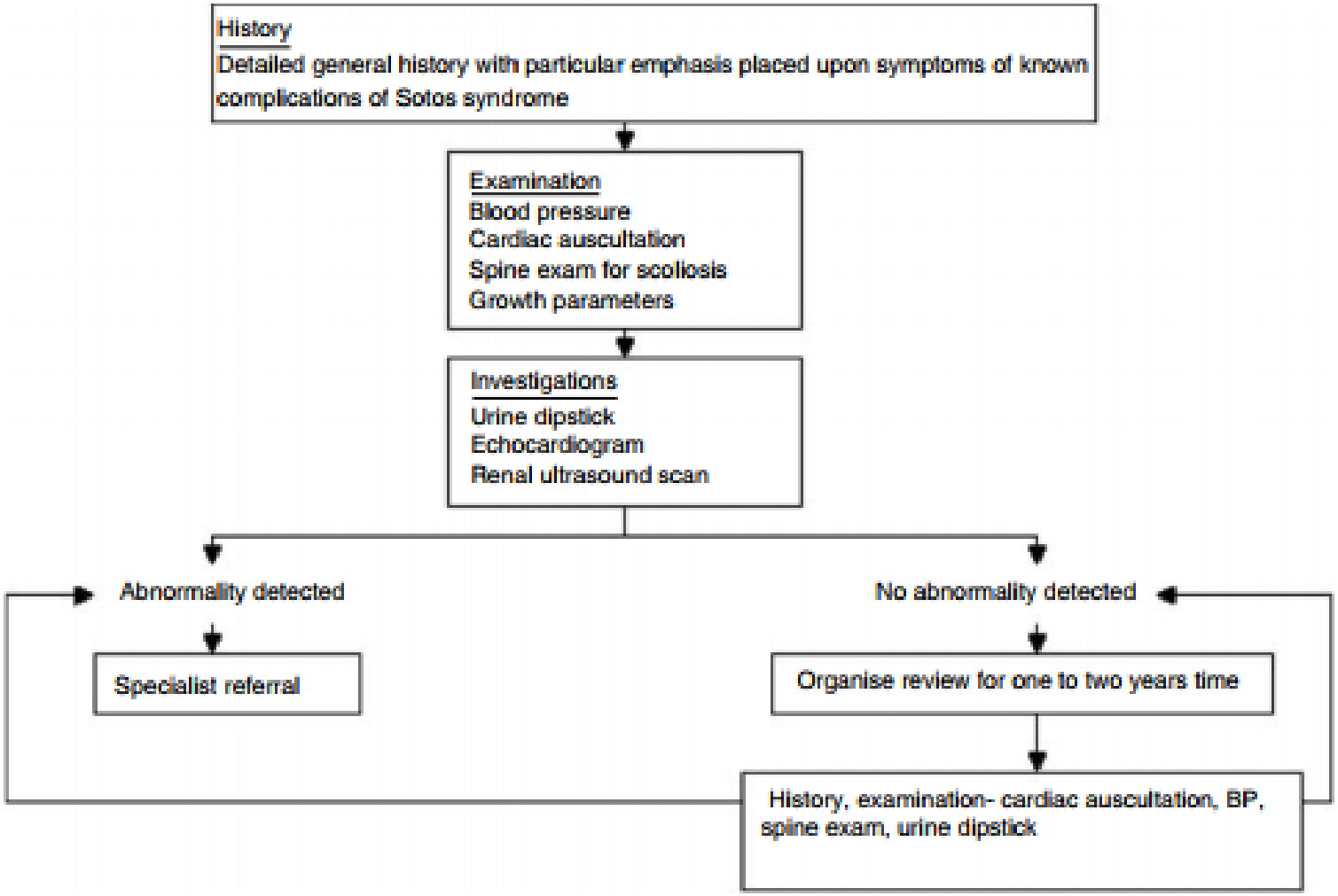
Additional report on Moreno-Nishimura-Schmidt overgrowth syndrome

A Novel Mosaic *NSD1* Intragenic Deletion in a Patient With an Atypical Phenotype

Am J Med Genet Part A 161A:611–618.

- Non iperaccrescimento
- RPM

Follow up


History
Detailed general history with particular emphasis placed upon symptoms of known complications of Sotos syndrome
Examination
Blood pressure
Cardiac auscultation
Spine exam for scoliosis
Growth parameters
Investigations
Urine dipstick
Echocardiogram
Renal ultrasound scan
Abnormality detected
No abnormality detected
Specialist referral
Organise review for one to two years time
History, examination- cardiac auscultation, BP, spine exam, urine dipstick

Sotos syndrome associated with Hirschsprung's disease: a new case and exome-sequencing analysis

Volume 82 | Number 1 | July 2017 Pediatric RESEARCH

Neonatal Cutis Laxa and Hypertrichosis Lanuginosa in Sotos Syndrome

Pediatric Dermatology Vol. 33 No. 6 e351–e352, 2016

NUOVI RISCONTRI

Sotos Syndrome: An Unusual Presentation with Intrauterine Growth Restriction, Generalized Lymphedema, and Intention Tremor

Am J Med Genet Part A 170A:1064–1069.

Severe Connective Tissue Laxity Including Aortic Dilatation in Sotos Syndrome

Am J Med Genet Part A 170A:531–535.

Pneumothorax from Subpleural Blebs—A New Association of Sotos Syndrome?

Am J Med Genet Part A 164A:1222–1226.

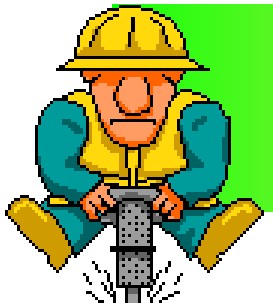
ATTENZIONE AL CONNETTIVO!

- ✓ AORTA
- ✓ CUTE
- ✓ PNX

Indicazione ad approfondire gli aspetti cardiovascolari

CONCLUSIONI

- Il solo criterio costante è la **gestalt facciale**, in associazione ad un numero variabile di criteri maggiori
- **Iperaccrescimento e macrocefalia** assoluti possono essere assenti, l'**età ossea** può non essere aumentata
- È alta la frequenza di **DIA** nei pazienti con mutazioni puntiformi
- Non complicanze cliniche di rilievo



PROPOSTE

Approfondire alcuni aspetti:

- **Visita infettivologia respiratoria**
- **Impedenzometria**
- **Polisonnografia**
- **Ecocardiogramma con specifiche misurazioni**
- **Valutazione odontoiatrica/OPT**

02.55032560

donatella.milani@policlinico.mi.it

Citazione

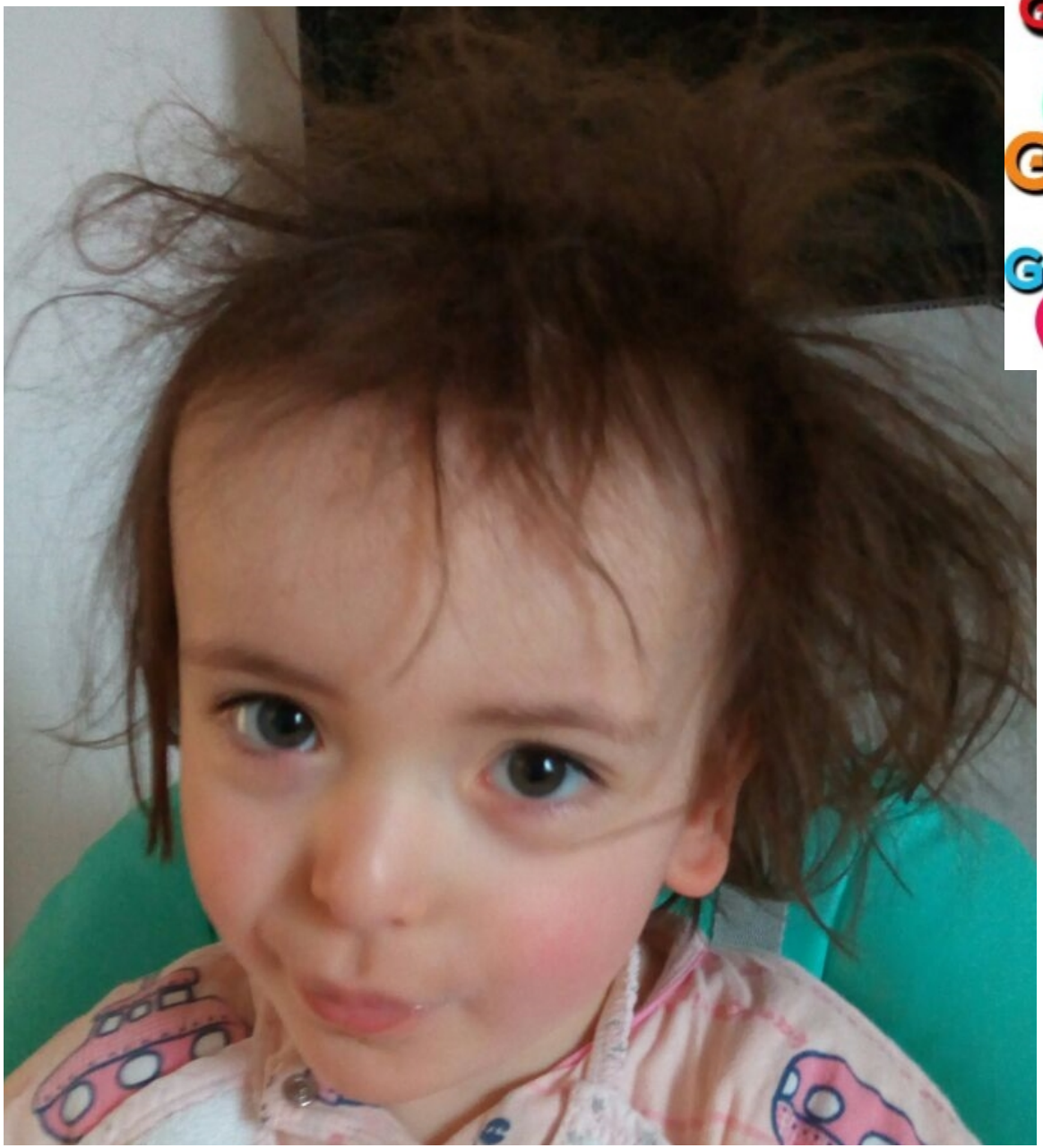
….e adesso parlo io…**Alessandro**..

Diciamocela tutta… questa storia di essere affetti da una patologia genetica rara, è una gran seccatura! Perché? Ve lo spiego subito.

Innanzitutto, ci sono troppe visite mediche da fare: hanno visitato più medici me in 5 anni di vita, che i miei genitori nei loro 65 anni cumulativi…ed io ODIO essere visitato, ODIO andare negli ospedali, in cui bisogna sempre fare delle attese lunghissimi e noiosissime, con mamma e papà che mi intimano continuamente di star buono…come se fosse facile… E poi quei dottori che ti toccano, ti auscultano, ti misurano, a volte senza troppa comprensione del fatto che io sia un bambino che non ha voglia di "collaborare". Per non parlare dei prelievi di sangue! Una tortura semestrale che proprio non riesco a capire. Unica misera consolazione: il regalo che mi comprano mamma e papà.

…noi spesso abbiamo genitori un po’ “pesanti”. Nel mio caso mi riferisco a mia madre, perché papà per fortuna è abbastanza rilassato. Mamma, invece, ciclicamente (come le stagioni) è preda di crisi di inadeguatezza, sensi di colpa per il tempo che toglie a me per lavorare, ansia da prestazione come educatrice.

Tirando le somme, credo proprio che essere affetti dalla Sindrome di Sotos sia una gran seccatura, ma anche una grande avventura e so anche che stupirò tutti, in barba a quel pezzetto di gene che si è perso chissà dove!



GRAZIE
Grazie