Sindrome di Sotos:
Correlazione genotipo-fenotipo

Domenico Coviello
Laboratorio Genetica Umana
E.O. Ospedali Galliera

XVIII Congresso Nazionale Associazione Gulliver

Monza
08 marzo 2014

Correlazione genotipo fenotipo

J Med Genet 1994;31:20–32

Original articles

Sotos syndrome: a study of the diagnostic criteria and natural history

Table 1 Conditions in which generalised or regional overgrowth may be present.

Weaver–Smith syndrome[3,4]
Marshall–Smith syndrome[5,6]
Simpson–Golabi–Behmel syndrome[7,8]
Ruvalcaba–Myhre–Smith syndrome[9,10]
Perlman syndrome[11,12]
Beckwith–Wiedemann syndrome[13,14]
SanFilippo syndrome[15]
Proteus syndrome[16,17]
Marfan syndrome[18]
Klinefelter syndrome[19]
Trisomy 8 mosaicism[20]
Fragile X syndrome[21]

Correlazione genotipo fenotipo

20

J Med Genet 1994;31:20–32

Original articles

Sotos syndrome: a study of the diagnostic criteria and natural history

T R P Cole, H E Hughes

Table 2 Protocol for categorising patients.

First assessment: facial gestalt alone	*Second assessment: facial gestalt plus data**
Group 1 Definitely Sotos	Group 1 Definitely Sotos
Group 2 Possibly Sotos	Group 2 Possibly Sotos
Group 3 Definitely not Sotos	Group 3 Definitely not Sotos

* Data provided on height, head circumference, developmental milestones, and bone age.

Correlazione genotipo fenotipo

20

J Med Genet 1994;31:20–32

Original articles

Sotos syndrome: a study of the diagnostic criteria and natural history

T R P Cole, H E Hughes

Table 3 Patient categories.

	Scoring on gestalt alone	*Rescored with data* to*		
		Group 1	*Group 2*	*Group 3*
Group 1	41	40	1	—
Group 2	16	—	7	9
Group 3	22	—	3	19
Total	79	40	11	28

* Data provided on height, head circumference, developmental milestones, and bone age.

Correlazione genotipo fenotipo

<u>Caratteristiche essenziali</u>
(presenti ≥90%)

Facies tipica
Disabilità intellettiva
Iperaccrescimento

<u>Caratteristiche frequenti</u>(presenti 15%-89%)

Disturbi comportamentali
Età ossea avanzata
Cardiopatia congenita
Anomalie cerebrali
Iperlassità ligamentosa / piattismo plantare
Preeclampsia materna in gravidanza
Complicanze neonatali
Anomalie renali congenite
Scoliosi
Epilessia / convulsioni febbrili

Correlazione genotipo fenotipo

American Journal of Medical Genetics 134A:247–253 (2005)

Mutation Analysis of the *NSD1* Gene in a Group of 59 Patients With Congenital Overgrowth

M. Cecconi,[1] F. Forzano,[1] D. Milani,[2] S. Cavani,[1] C. Baldo,[1] A. Selicorni,[2] C. Pantaleoni,[3] M. Silengo,[4] G.B. Ferrero,[4] G. Scarano,[5] M. Della Monica,[5] R. Fischetto,[6] P. Grammatico,[7] S. Majore,[7] G. Zampino,[8] L. Memo,[9] E. Lucci Cordisco,[10] G. Neri,[10] M. Pierluigi,[1] F. Dagna Bricarelli,[1] M. Grasso,[1] and Francesca Faravelli[1]*

The phenotypic characterization of patients with a mutant NSD1 genotype suggests that the most consistent finding in Sotos syndrome is represented by the typical facial gestalt (Fig. 2), in association with a variable number of additional major criteria. In our series, a height above the 97th centile was absent in five mutated patients (5/17, 30%), absolute macrocephaly in two (2/17, 12%), advanced bone age was not significantly advanced in three, and corresponded to chronological age in two (5/17, 30%). It is of interest to mention that,

Correlazione genotipo fenotipo

American Journal of Medical Genetics 134A:247–253 (2005)

Mutation Analysis of the *NSD1* Gene in a Group of 59 Patients With Congenital Overgrowth

M. Cecconi,[1] F. Forzano,[1] D. Milani,[2] S. Cavani,[1] C. Baldo,[1] A. Selicorni,[2] C. Pantaleoni,[3] M. Silengo,[4] G.B. Ferrero,[4]

TABLE III. Clinical Manifestations in Patients With NSD1 Aberrations

Patient	Mutation	Sex	Age at last control	Facial gestalt	Height >97th	Macrocephaly	Advanced bone age	Developmental delay	Seizures	Heart defect	Orthopedic features	Genitourinary abnormalities	Other	MRI abnormalities
1	4497G > C	M	4 years 4 months	Sotos	–	+	–/+		–	–		–	–	np
2	5509G > C	F	9 years	Sotos	+	+	+	–	–	ASD	–	–	–	VM, HyCC Chiari I
3	IVS19 + 1delGTAA	F	10 years	Sotos	+	+	+	+	–	ASD	–	+	–	–
4	1697delG	M	1 year 8 months	Sotos	–	–	+	+/–	–	ASD	–	–	–	–
5	2386delGAAA	F	7 years 1 month	Sotos	+	+	+	+	+	ASD,VSD, PDA,CoA	Flat feet	–	–	VM
6	2386delGAAA	M	13 years	Sotos	+	+	+	+/–	+	–	Flat feet, scoliosis	–	–	–
7	2407delC	M	9 years 6 months	Sotos	+	+	+	+/–	–	–	–	–	–	VM, HyCC
8	3062delG	M	4 years 7 months	Sotos	+	+	+	+	–	–	Severe pectus excavatum, scoliosis	+	–	VM, HyCC
9	4773delTA	M	11 years	Sotos	+	+	+	+/–	–	–	–	–	–	–
10	7514delA	M	7 years 5 months	Sotos	+	+	–	+	–	PDA,ASD, right branch block	Bilateral tibia vara	–	Inguinal hernia	VM
11	1318C > T	F	3 years 5 months	Sotos	+	+	+	–	–	–	–	+	–	np
12	1894C > T	F	7 years	Sotos	+	+	–	–	–	–	Scoliosis	–	–	–
13	5950C > T	F	4 years 10 months	Sotos	–	+	+	+	–	ASD	Abnormal vertebral body D7	–	Hypothyroidism	VM
14	1727insA	F	6 years 6 months	Sotos	–	+	+	+/–	+	–	Left hand post-axial polydactyly	–	–	VM
15	2516-7delTGins13	F	8 years 6 months	Sotos	–	–	+	+	–	ASD	Scoliosis	–	–	np
16	2943-4insT	M	2 years	Sotos	+	+	–/+	+	–	–	–	–	–	np
17	Deletion	M	9 years	Sotos	–	–	+	+	–	–	–	–	–	HyCC

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; CoA, aortic coarctation; np, not performed; VM, ventriculomegaly; HyCC, hypoplastic corpus callosum.

Correlazione genotipo fenotipo

Am. J. Hum. Genet. 77:193–204, 2005

Genotype-Phenotype Associations in Sotos Syndrome: An Analysis of 266 Individuals with *NSD1* Aberrations

We identified 266 individuals with intragenic *NSD1* mutations or 5q35 microdeletions encompassing *NSD1* (referred to as "*NSD1*-positive individuals"), through analyses of 530 subjects with diverse phenotypes. Truncating *NSD1* mutations occurred throughout the gene, but pathogenic missense mutations occurred only in functional domains ($P < 2 \times 10^{-16}$). Sotos syndrome was clinically diagnosed in 99% of *NSD1*-positive individuals, independent of the molecular analyses, indicating that *NSD1* aberrations are essentially specific to this condition. Furthermore, our data suggest that 93% of patients who have been clinically diagnosed with Sotos syndrome have identifiable *NSD1* abnormalities, of which 83% are intragenic mutations and 10% are 5q35 microdeletions. We reviewed the clinical phenotypes of 239 *NSD1*-positive individuals. Facial dysmorphism, learning disability, and childhood overgrowth were present in 90% of the individuals. However, both the height and head circumference of 10% of the individuals were within the normal range, indicating that overgrowth is not obligatory for the diagnosis of Sotos syndrome. A broad spectrum of associated clinical features was also present, the occurrence of which was largely independent of genotype, since individuals with identical mutations had different phenotypes. We compared the phenotypes of patients with intragenic *NSD1* mutations with those of patients with 5q35 microdeletions. Patients with microdeletions had less-prominent overgrowth ($P = .0003$) and more-severe learning disability ($P = 3 \times 10^{-9}$) than patients with mutations. However, all features present in patients with microdeletions were also observed in patients with mutations, and there was no correlation between deletion size and the clinical phenotype, suggesting that the deletion of additional genes in patients with 5q35 microdeletions has little specific effect on phenotype. We identified only 13 familial cases. The reasons for the low vertical transmission rate are unclear, although familial cases were more likely than nonfamilial cases ($P = .005$) to carry missense mutations, suggesting that the underlying *NSD1* mutational mechanism in Sotos syndrome may influence reproductive fitness.

Correlazione genotipo fenotipo

Table 3

Clinical Features of Patients with Recurrent *NSD1* Mutations

Mutation and Patient ID	Clinical Feature(s)[a]
2386-9delGAAA:	
COG300	Severe LD, seizures, scoliosis, scaphocephaly
COG514	Moderate LD, seizures, ASD, VSD, PDA
COG523	Moderate LD, scoliosis
3549-50insT:	
COG073	Severe LD, seizures, complex cardiac anomaly, duplex kidney, hypercalcemia
COG095	Moderate LD, seizures, scoliosis
5279-82delTCTG:	
COG252	LD[b], ASD, scoliosis
COG288	Mild LD, conductive hearing loss
COG455	Mild LD
6596delG:	
COG265	Moderate LD, scoliosis, constipation, fixed flexion deformity of knees
COG272	Mild LD, seizures
R440X:	
COG196	No LD, bicuspid aortic valve, left pyelectasia
COG494	Moderate LD, strabismus, hyperlaxity, pectus excavatum
R604X:	
COG022	Mild LD, seizures, ASD
COG054	Mild LD, cardiac anomaly, scoliosis, strabismus
COG154	Severe LD, VSD, VUR, GOR, laryngomalacia
R611X:	
COG088	Mild LD, seizures, VSD
COG223	Moderate LD, scoliosis
R1021X:	

Table 3 (continued)

Mutation and Patient ID	Clinical Feature(s)[a]
C1925R:	
COG034	Moderate LD, scoliosis
COG144	Mild LD, scoliosis, pectus carinatum, strabismus
R1952W:	
COG371	Mild LD, hemihypertrophy, hepatomegaly
COG434	Severe LD, TGA, scoliosis, cutis laxa
R1984Q:	
COG463	Mild LD, seizures, cardiac anomaly, chiari malformation
COG464	Moderate LD, ASD
COG490	Moderate LD, seizures, scoliosis
COG628	LD[b], cryptorchidism, phimosis
Y1997C:	
COG233	Moderate LD, scoliosis, pectus excavatum, hypospadias
COG491	Severe LD
R2017W:	
COG308	Mild LD, scoliosis, strabismus
COG500	Moderate LD, scoliosis, VUR
IVS9+3-6delGAGT:	
COG134	Moderate LD, VUR
COG227	Moderate LD, seizures, scoliosis, inguinal hernia, scaphocephaly

NOTE.—ASD = atrial septal defect; GOR = gastroesophageal reflux; PDA = patent ductus arteriosus; PUJ = pelviureteric junction; TGA = transposition of the great arteries; VSD = ventricular septal defect; VUR = vesicoureteral reflux.

[a] In addition to dysmorphism and overgrowth. LD = learning disability.

Correlazione genotipo fenotipo

A Clinical Study of Sotos Syndrome Patients With Review of the Literature

George Leventopoulos, MD, Sophia Kitsiou-Tzeli, MD, PhD, Konstantinos Kritikos, MD, Stavroula Psoni, MD, Ariadni Mavrou, PhD, Emmanuel Kanavakis, MD, PhD, and Helen Fryssira, MD, MSc, PhD

Sotos syndrome is characterized by tall stature, advanced bone age, typical facial abnormalities, and developmental delay. The associated gene is *NSD1*. The study involved 22 patients who fulfilled the clinical criteria. Phenotypic characteristics, central nervous system findings, and cardiovascular and urinary tract abnormalities were evaluated. Meta-analysis on the incidence of cardinal clinical manifestations from the literature was also performed. Macrocephaly was present in all patients. Advanced bone age was noted in 14 of 22 patients (63%), and its incidence presented significant statistical difference in the meta analysis of previous studies. Some patients had serious clinical manifestations, such as congenital heart defects, dysplastic kidneys, psychosis, and leukemia. Clinical and laboratory examinations should be performed to prevent and manage any unusual medical aspect of the syndrome. Facial gestalt and macrocephaly, rather than advanced bone age, are the strongest indications for clinical diagnosis.

Pediatr Neurol 2009;40:357-364.

Correlazione genotipo fenotipo

Table 2. Clinical and laboratory findings in 19 patients with Sotos syndrome (present study)

Characteristic	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age*	4.5 yr	1.5 yr	2.5 yr	7 yr	2 mo	6 mo	3 yr	3.5 yr	4 mo	4 mo	2 mo	1.5 yr	5 mo	5 mo	3 yr	14 mo	1 yr	12 yr	5.5 yr
Sex	M	F	M	F	M	M	M	F	F	F	M	F	M	F	M	F	M	F	F
Facial features																			
Prominent forehead	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Macrocephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dolichocephaly	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–
Down slant palpebral fissures	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–
Hypertelorism, epicanthus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Pointed chin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
High palate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Premature eruption of teeth	–	+	+	–	–	+	+	+	+	–	–	+	–	–	–	+	–	+	–
Developmental																			
Mental retardation (severe: IQ < 50)	–	–	+	+	–	+	+	+	–	–	–	–	–	+	+	+	–	–	+
Psychomotor retardation	+	–	+	–	–	–	+	–	–	–	–	–	–	–	+	+	–	+	+
Neonatal hypotonia	–	+	–	–	–	+	–	–	–	–	+	+	+	–	+	–	+	–	–
Growth																			
Birth weight, g (gestational age, wk)	2120† (37)	1250† (29)	n/a	n/a	†	3185	3800	n/a	n/a	n/a	4300	2780 (36)	4425	4170	2650 (35)	n/a	4100	3650	4340
Somatometric large	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+
Bone age‡	D	A	D	A	N	N	A	A	D	N	A	A	A	A	A	A	N	A	A
Brain abnormalities, MRI	+	+	+	N	+	N	+	+	+	+	N	+	+	N	+	+	+	+	N
Urinary malformation	+	+	–	–	+	+	–	–	–	–	–	–	+	–	+	–	+	–	–
Congenital heart defect§	–	PFO	–	–	PFO	VSD	–	–	–	–	–	–	–	ASD	–	–	–	–	–

Correlazione genotipo fenotipo

European Journal of Human Genetics (2006), 1–8

1018-4813/06 $30.00
www.nature.com/ejhg

PRACTICAL GENETICS

In association with orphanet

Sotos syndrome

Sotos syndrome is an autosomal dominant condition characterised by a distinctive facial appearance, learning disability and overgrowth resulting in tall stature and macrocephaly. In 2002, Sotos syndrome was shown to be caused by mutations and deletions of *NSD1*, which encodes a histone methyltransferase implicated in chromatin regulation. More recently, the *NSD1* mutational spectrum has been defined, the phenotype of Sotos syndrome clarified and diagnostic and management guidelines developed.

Correlazione genotipo fenotipo

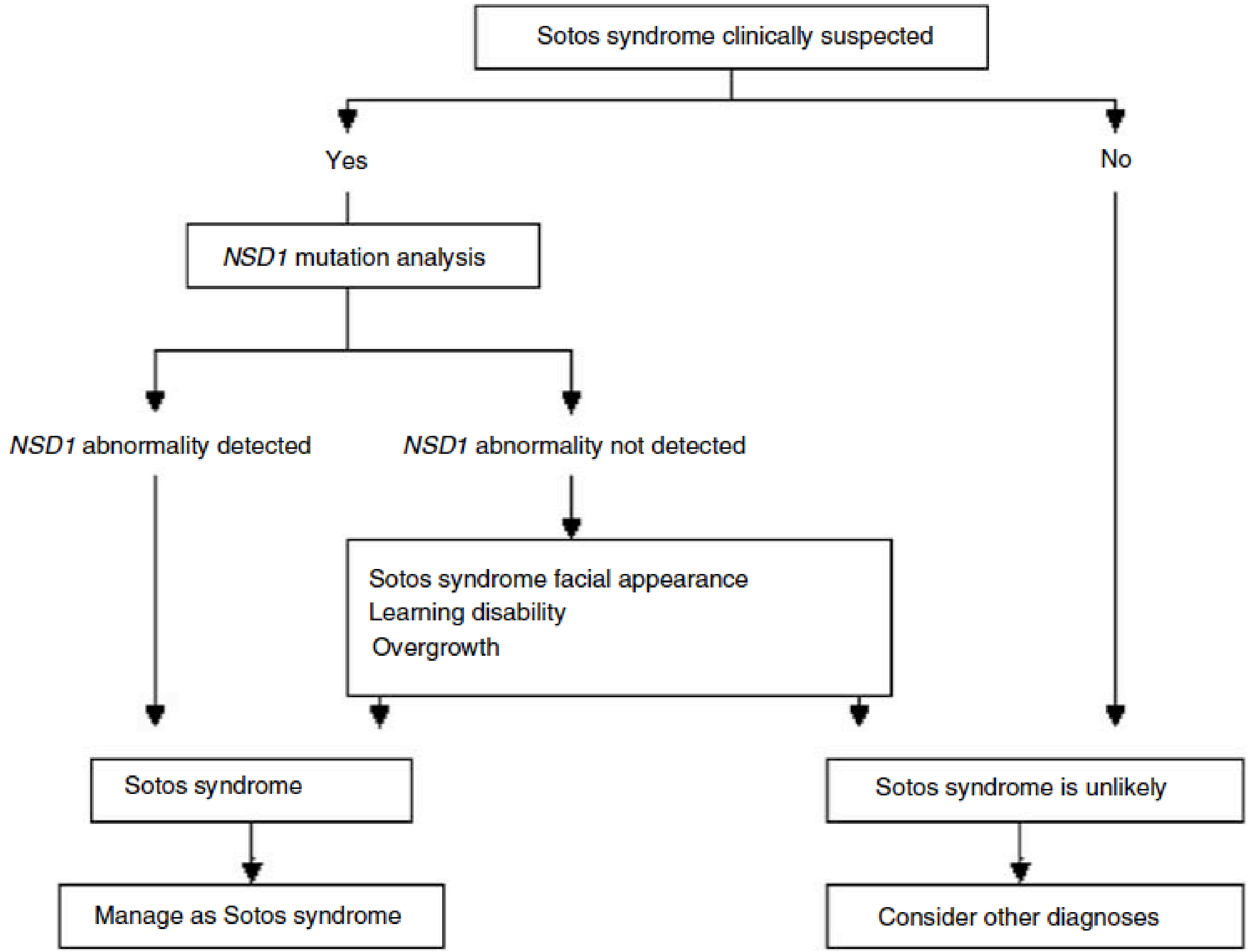


Figure 1 Diagnostic strategy for individuals in which a diagnosis of Sotos syndrome is suspected.

Correlazione genotipo fenotipo

Table 3 Conditions that may be considered in the differential diagnosis of Sotos syndrome

Condition	*OMIM#*	*Clinical features*	*Inheritance pattern*	*Gene*
Weaver syndrome	277590	Tall stature, macrocephaly, advanced bone age, learning disability, broad forehead with macrocephaly, hypertelorism, 'stuck-on' chin, horizontal chin crease, metaphyseal changes on X-ray	Autosomal dominant	Unknown
Bannayan-Riley-Ruvalcaba syndrome	153480	Macrocephaly, learning disability, lipomatosis, haemangiomatosis and pigmented macules on the shaft of the penis	Autosomal dominant	PTEN
Beckwith-Wiedemann syndrome	130650	Tall stature, abdominal wall defects, macroglossia, ear lobe creases, helical pits, visceromegaly, hemihypertrophy, neonatal hypoglycaemia, renal abnormalities and embryonal tumours	Imprinted	Abnormalities of 11p15 region
Simpson-Golabi-Behmel syndrome	312870	Pre- and post-natal overgrowth, learning disability, hypertelorism, downslanting palpebral fissures, epicanthic folds, short nose, macrostomia, macroglossia, supernumerary nipples	X-linked recessive	GPC3
Benign familial macrocephaly	153470	Macrocephaly in an individual who is otherwise neurologically normal	Autosomal dominant	Unknown
Fragile X syndrome	309550	Tall stature, macrocephaly, learning disability, prominent forehead, prominent mandible, mid-face hypoplasia, large ears, large testes	X-linked recessive	FMR1
Marfan syndrome	154700	Tall stature, arachnodactyly, pectus deformities of the chest, mitral or aortic regurgitation, ectopic lentis and mild joint laxity	Autosomal dominant	FBN1
Marshall-Smith syndrome	602535	Advanced bone age, increased birth length with subsequent failure to thrive, prominent forehead, prominent eyes, micrognathia and anteverted nares, broad proximal and middle phalanges	Unknown	Unknown
Nevo syndrome	601451	Pre-natal overgrowth, advanced bone age, macrocephaly, large extremities, pedal oedema, wrist drop, contractures and learning disability	Autosomal recessive	PLOD1

Correlazione genotipo fenotipo

Genotype–phenotype associations

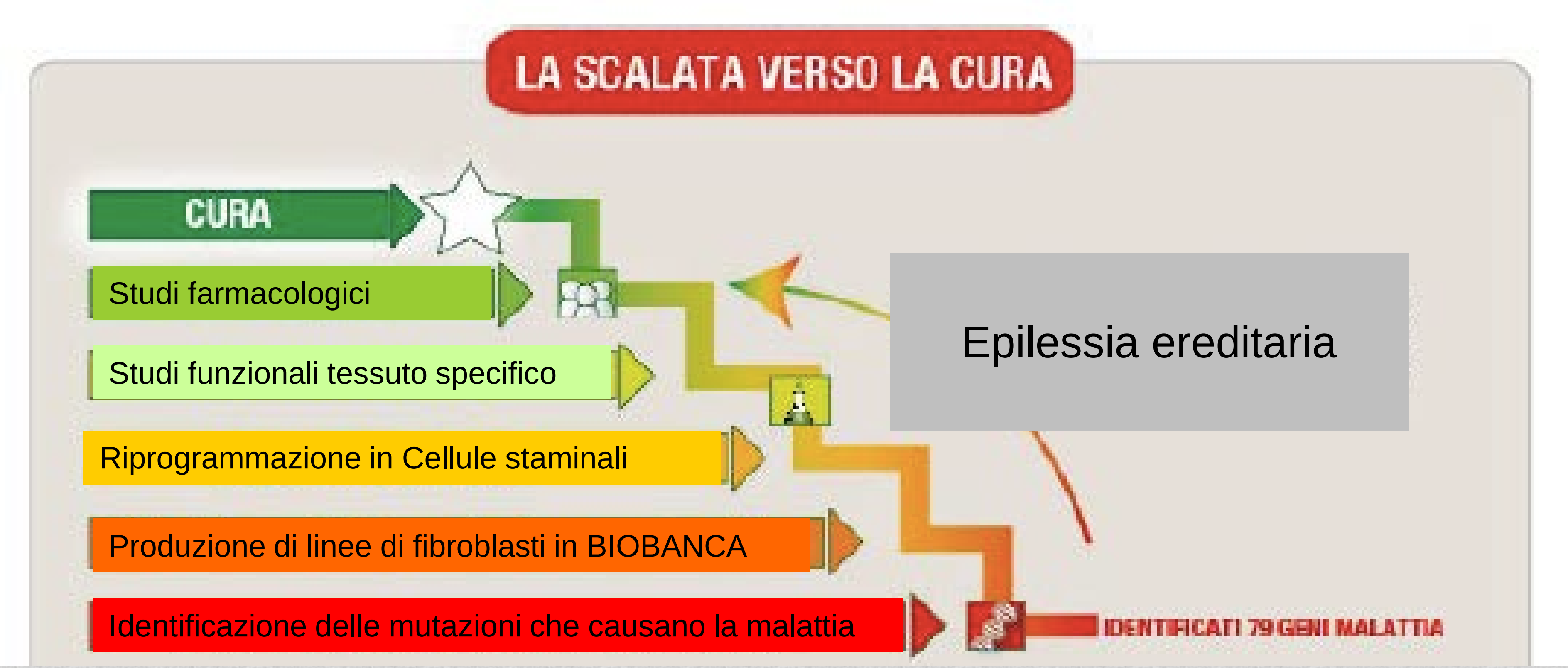
There is no correlation between mutation position and clinical phenotype and the very broad clinical variability of Sotos syndrome appears independent of genotype as cases with identical mutations often have different clinical features.[10] 5q35 microdeletion cases are significantly more likely to have severe learning disability than cases with intragenic mutations and also tend to have less pronounced overgrowth.[10] This is likely due to the generic effects of microchromosomal defects that are typically associated with learning disability and short stature throughout the genome.[30] There is no evidence that deletion of neighbouring genes in 5q35 microdeletion cases has any specific effect on phenotype and all features observed in microdeletion cases have also been reported in individuals with intragenic *NSD1* mutations.[10,25]

Conclusioni

- S. Sotos malattia AD, penetranza 100%
- Casi Sporadici, (casi familiari rarissimi)
- Mutazioni in NSD1 sono presenti nel 70 - 93% dei pazienti con s. Sotos
- NO hot spot di mutazioni
- Ad oggi mai riscontrati casi di mosaicismo gonadico; RR < 1%
- NO mutazioni NSD1 in pazienti con iperaccrescimento ma senza caratteristiche cliniche facciali.
- Mutazioni in NSD1 in pazienti con tipiche manifestazioni facciali ma senza iperaccrescimento o macrocefalia.
- Mutazioni/microdelezioni nel gene NSD1 sono altamente specifiche del fenotipo Sotos. Mai riscontrate in iperaccrescimento aspecifico.
- Una Check list accurata con rigorosi criteri clinici per l'accesso al test potrebbe fornire una guida utile per migliorare l'appropriatezza del test genetico.

Futuro ?

Ricerca nelle malattie rare



Grazie per l'attenzione

E.O. Ospedali Galliera