Associazione Nazionale di Volontariato Cornelia de Lange

Congresso Nazionale
Associazione di Volontariato
S. di Cornelia de Lange
Pesaro,26-28 settembre 2014

Associazione Nazionale di Volontariato Cornelia de Lange

Qualche domanda sulla sindrome di Cornelia de Lange

Dott Angelo Selicorni

Ambulatorio di Genetica Clinica Pediatrica

FONDAZIONE MONZA E BRIANZA PER IL BAMBINO E LA SUA MAMMA

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA
FACOLTÀ DI MEDICINA E CHIRURGIA
CLINICA PEDIATRICA
Direttore: Prof. Andrea Biondi

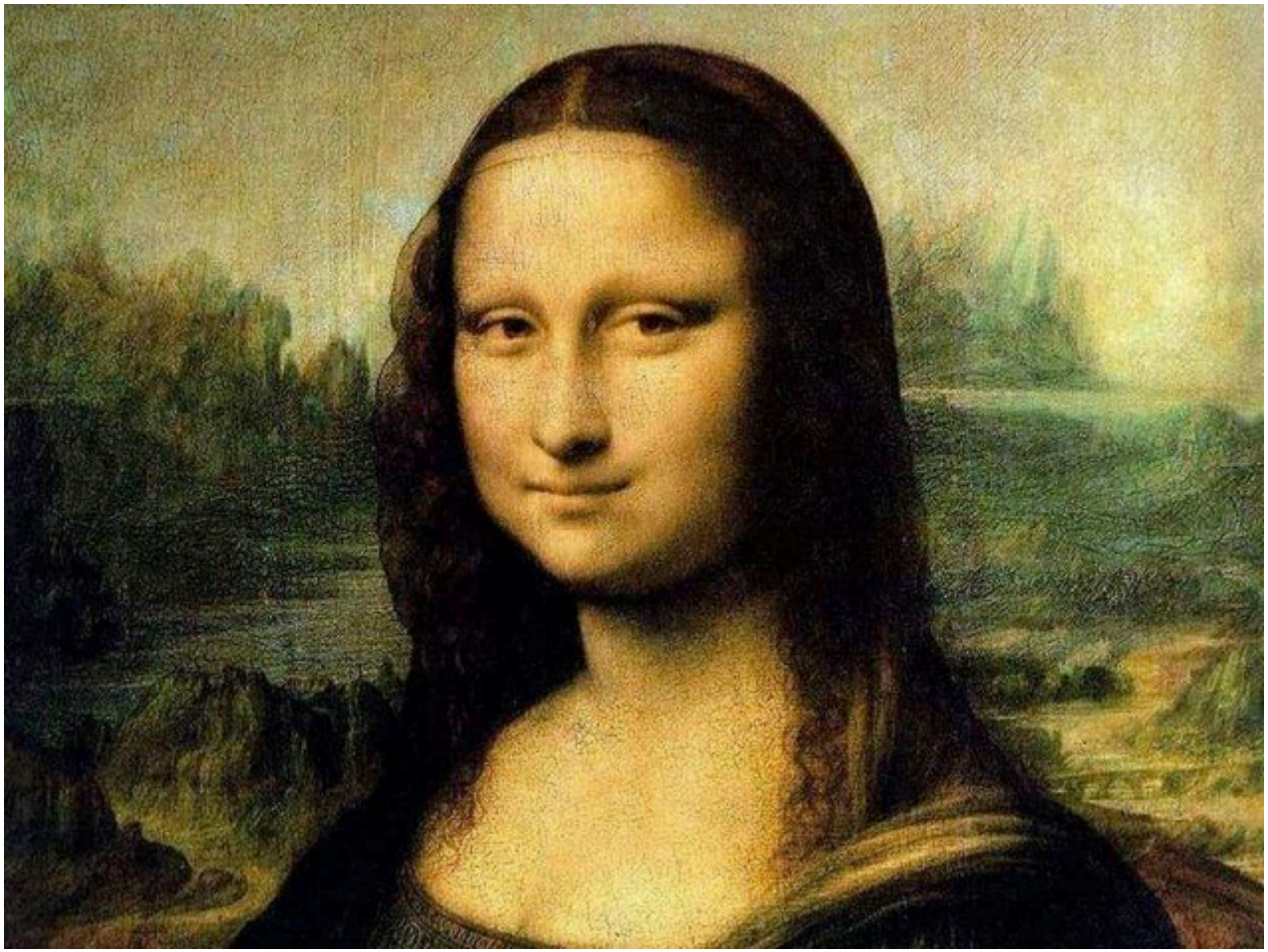
Azienda Ospedaliera San Gerardo

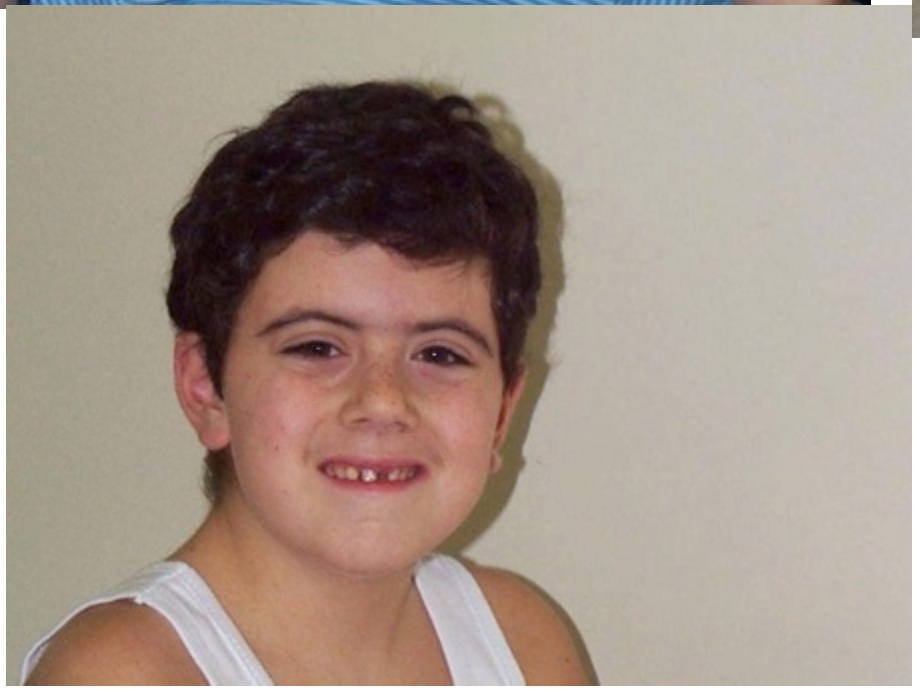
Come si sospetta e si pone la diagnosi di CdLS ?

S. di Cornelia de Lange

- Condizione clinica multi sistemica che coinvolge:
  * crescita in peso e altezza
  * sviluppo psico-motorio ed intellettivo
  * possibile presenza di malformazioni maggiori
  * possibile presenza di complicanze mediche
  * presenza di caratteristiche somatiche specifiche

Si riconosce ciò che si conosce





Dalla clinica alla genetica

Sospetto clinico

↓

Attivazione test genetico

↓

Conferma genetica, oggi possibile «solo» nel 70% dei pazienti

Dalla clinica alla genetica

a) Esiste un numero significativo di bambini in cui, pur essendo certa la diagnosi clinica, non vi è ancora una conferma molecolare

b) per queste famiglie l'evoluzione delle conoscenze potrà portare ad una definizione in un futuro +/- prossimo

Come cresce un bambino con la de Lange ?

www.cdlsusa.org

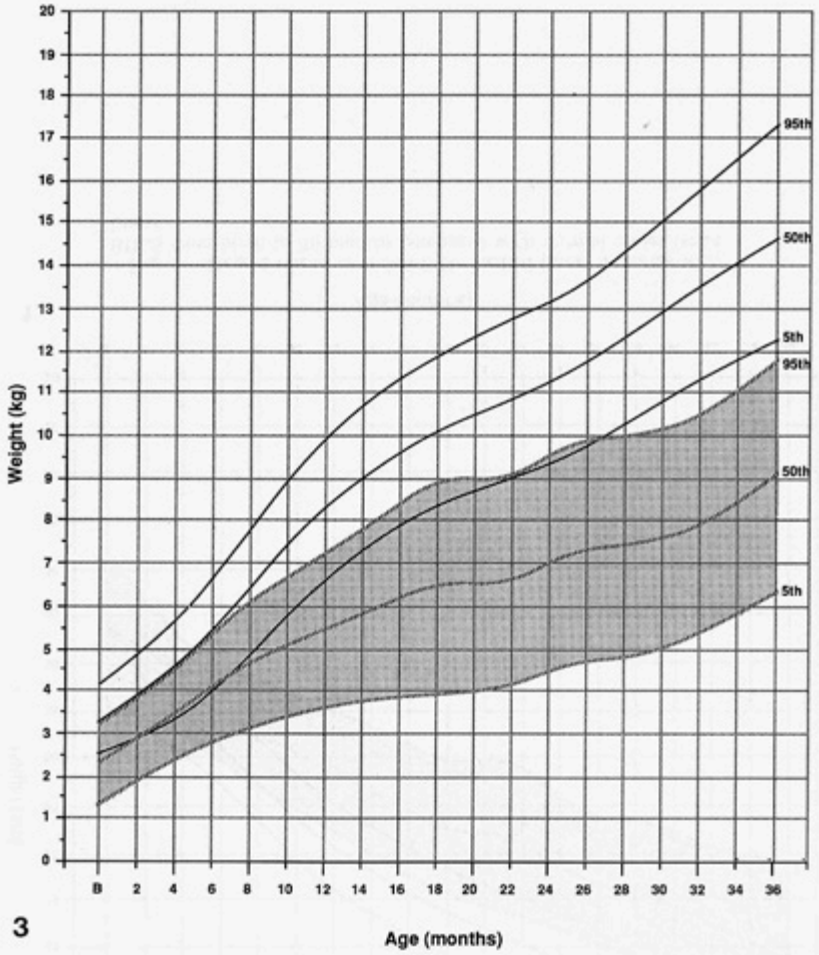


Fig. 3. Weight (mean ± 1.645 S.D., dashed lines) in males with BDLS from birth to 36 months compared with normal males (solid lines).

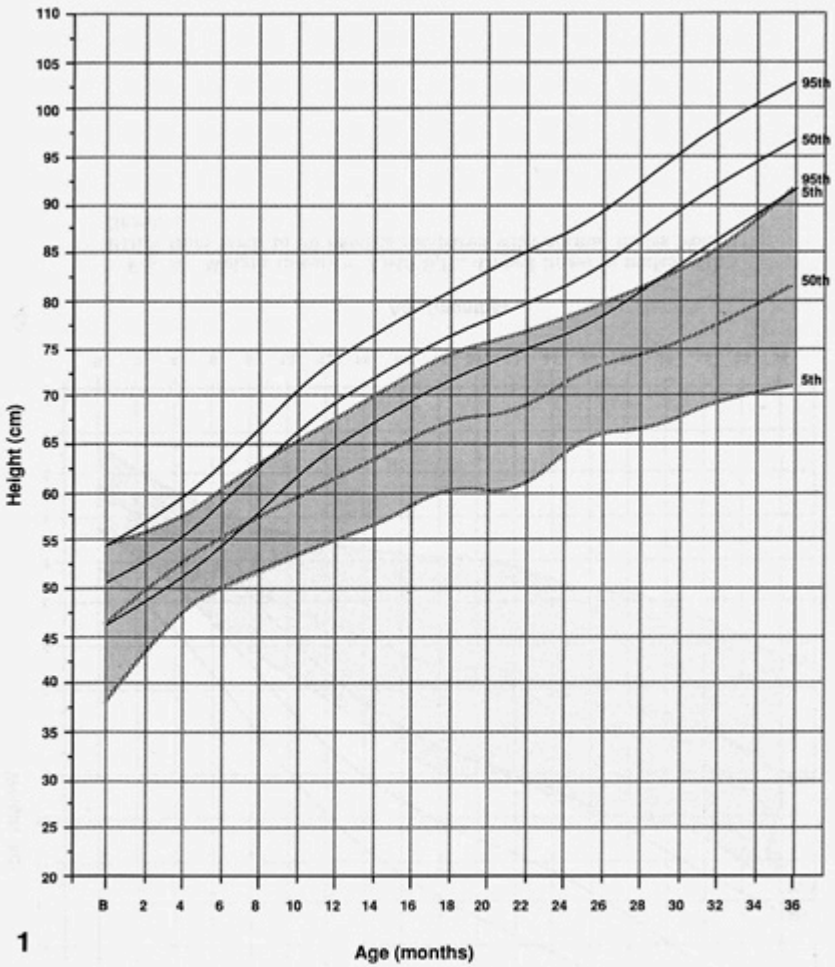
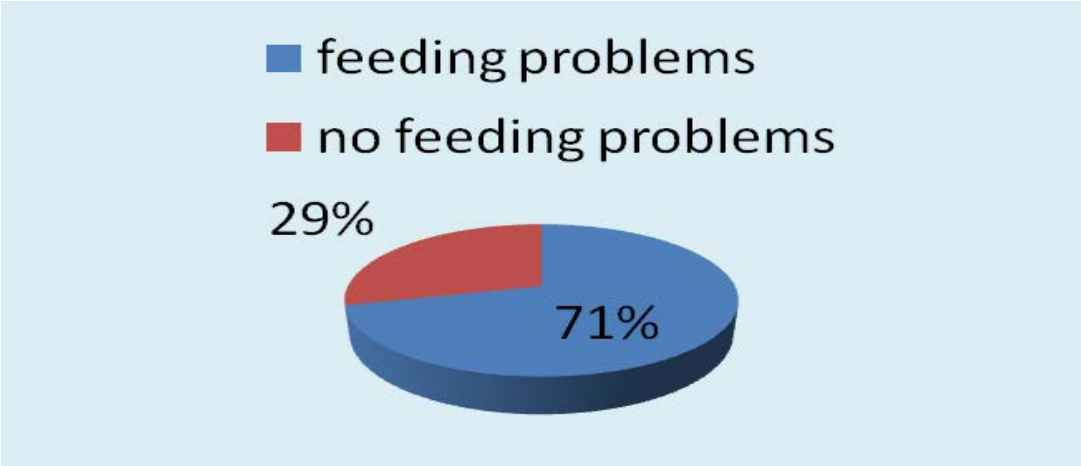
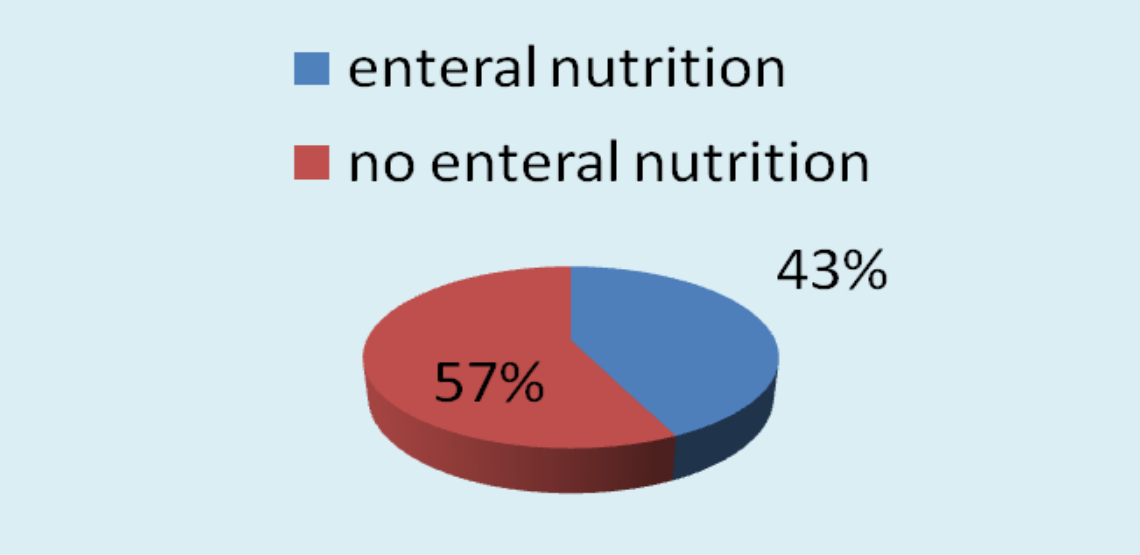


Fig. 1. Height (mean ± 1.645 S.D., dashed lines) in males with BDLS from birth to 36 months compared with normal males (solid lines).

Un problema da considerare: disturbi della deglutizione





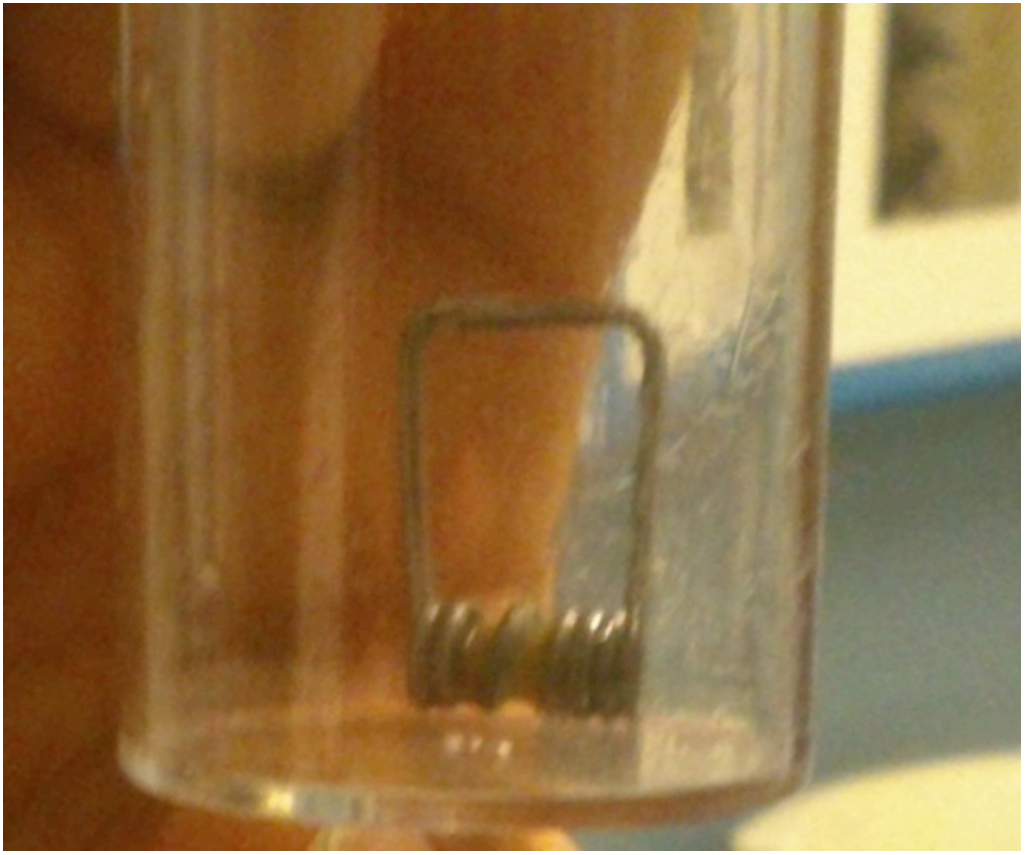
In prospettiva……..

La grandissima parte dei bambini impara ad assumere cibo spontaneamente indipendentemente dal grado di «gravità»

Una quota significativa di pazienti giovani adulti sviluppa un quadro di sovrappeso e/o franca obesità

REPLAY AND SONS

Il «cibo» di alcuni vostri campioni !!!!



Quali problemi medici può avere un bambino con la de Lange ?

Due categorie di problemi

- Malformazioni maggiori => o sono presenti sin dalla nascita o non saranno mai presenti

- Complicanze mediche => monitoraggio clinico/strumentale nel corso della vita di ogni bambino/ragazzo CdLS

Malformazioni maggiori

Tabella I Prevalenza delle malformazioni

Tipo di malformazione maggiore	Percentuale di osservazione
Cardiopatia congenita	circa 25-30%
Palatoschisi	10%
Malformazione oculare	descritta ma non definita
Malformazione del SNC	descritta ma non definita
Malformazione renale/ vie urinarie	12-40%
Malformazione gastro-intestinale (malrotazione intestinale)	descritta ma non definita
Anomalia genitale (criptorchidismo)	33%
Ernia diaframmatica	rara

Regola fondamentale

Le complicanze mediche descritte si riferiscono SOLO ad un rischio aumentato NON rappresentano una certezza di insorgenza

American Journal of Medical Genetics 119A:283–287 (2003)

Gastroesophageal Reflux and Cornelia de Lange Syndrome: Typical and Atypical Symptoms

S. Luzzani,[2] F. Macchini,[2] A. Valadè,[2] D. Milani,[1] and A. Selicorni[1]*
[1]*I Paediatric Department, University of Milan, Milan, Italy*
[2]*Paediatric Surgery Department, ICP Milan, Milan, Italy*

Il Reflusso Gastro-Esofageo è una complicanza frequente della patologia (28/43 = 65%)

-E' spesso accompagnato da una importante sintomatologia comportamentale (iperattività, auto ed etero aggressività)

TABLE V. Frequency of Typical and Atypical GER Symptoms at the First Evaluation

Symptoms	No. of patients	Classical cases	Mild cases
a. Typical symptoms			
Regurgitation	9	3	6
Vomiting	15	7	8
Refusal of food	8	6	2
Infection of respiratory tract	10	6	4
Cough	3	1	2
b. Atypical symptoms			
Bruxism	10	6	4
Nocturnal agitation	14	7	7
Hyperactivity	24	12	12
Self injurious behavior	8	5	3

Resuts of medical treatment

TABLE IX. Results of Anti-Reflux Therapy as Results From the Endoscopic Examinations Performed During the Follow-Up

Evolution of GER after treatment	Number
Worsened	0
Same	0
Improved	10
Disappeared	15
Spontaneously solved	3

TABLE X. Evolution of the Typical GER Symptoms During the Follow-Up

Symptoms	Unchanged	Improved	Disappeared
Regurgitation	2	3	4
Vomiting	3	3	9
Refusal of food	0	2	6
Infection of respiratory tract	1	2	7
Cough	1	0	2

TABLE XI. Evolution of the Atypical GER Symptoms During the Follow-Up

Symptoms	Unchanged	Improved	Disappeared
Bruxism	4	4	2
Nocturnal agitation	3	6	5
Hyperactivity	0	14	10
Self injurious behavior	0	5	3

REGULAR ARTICLE

Barrett's esophagus and Cornelia de Lange Syndrome

Francesco Macchini (francesco.macchini@unimi.it)[1], Giorgio Fava[2], Angelo Selicorni[3], Maurizio Torricelli[1], Ernesto Leva[1], Alberto Valadè[1]

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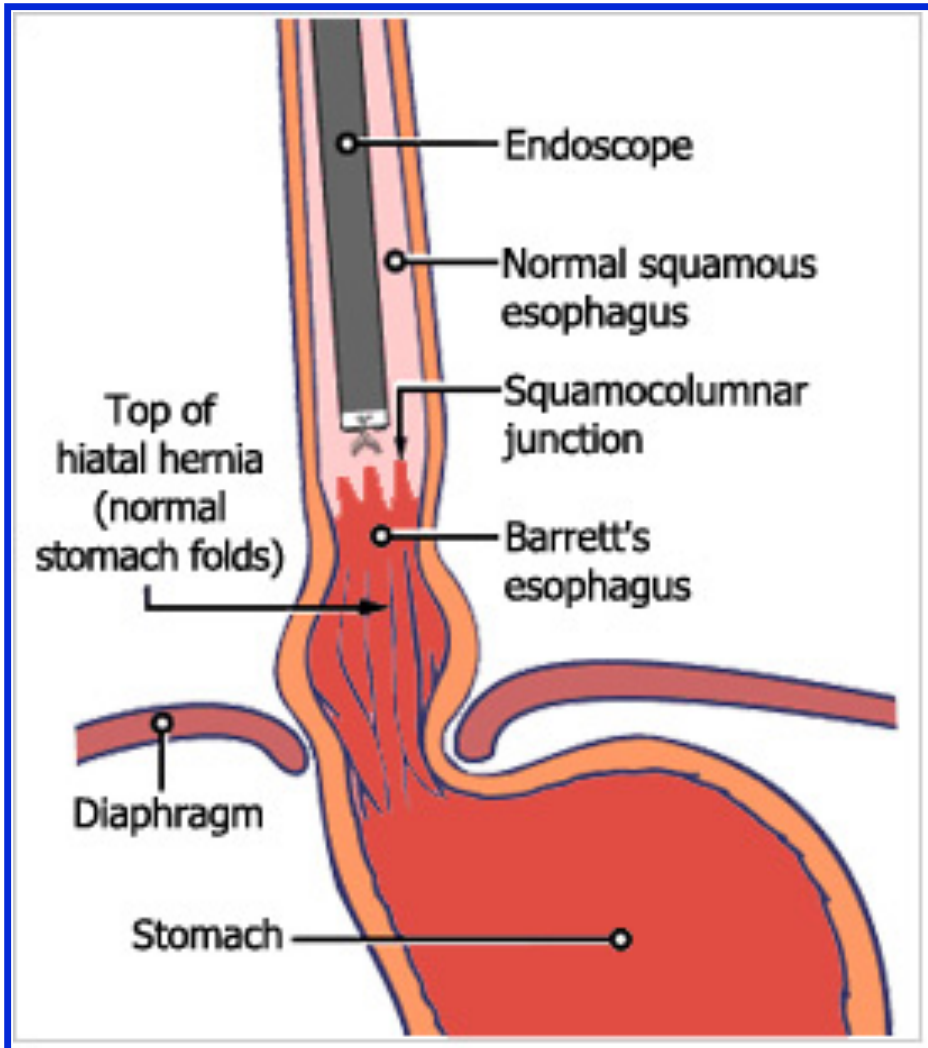
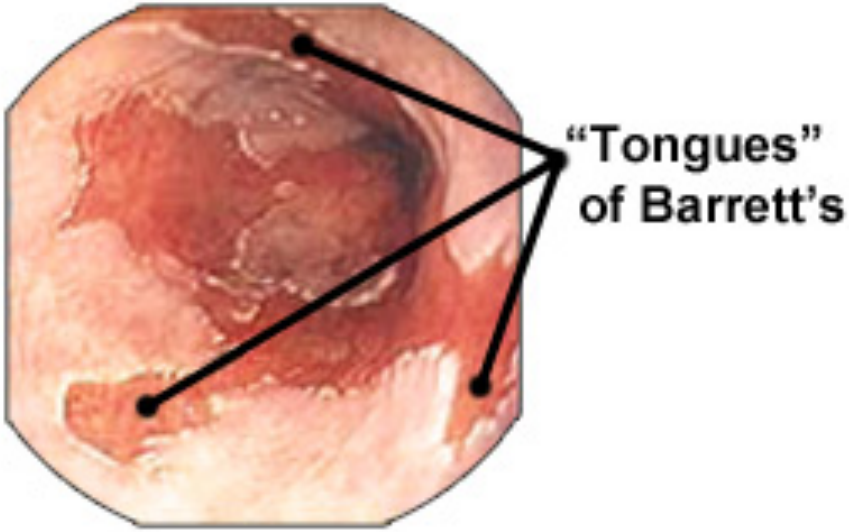
3.1st Pediatric Department, University of Milan, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy

62 pazienti studiati

Results: Gastro-oesophageal reflux disease was found in 50 CDLS patients (80%) and BE in six of them (12% of the GERD group, 9.6% of the entire population, mean age 17 years, range 6–32 years). A short segment BE was observed in three patients, a long one in two patients and an infiltrating adenocarcinoma of the lower oesophagus in one patient.

Conclusions: A higher frequency of BE in CDLS patients than in a normal population is found. A delayed diagnosis because of atypical GERD symptoms and an altered intestinal motility as a result of neurological impairment can be recognized as the main cause.





Actual endoscopic photo

Photo courtesy of the Seattle Barrett's Esophagus Research Program

Follow-up dei pz con BE

Table 2 Main characteristics of BE in CDLS patients (follow-up 3.5 years)

Patient	Sex	Age (years)	BE	Endoscopy	Therapy	Outcome
1	M	16	Metaplasia	Short segment	PPI	Regression of metaplasia
2	F	6	Metaplasia	Short segment	PPI	Regression of metaplasia
3	M	22	Metaplasia	Short segment	PPI	Regression of metaplasia
4	M	6	Metaplasia	Long segment	PPI+ fundoplication + mucosal ablation	Regression of metaplasia
5	M	32	Metaplasia	Long segment	PPI+ fundoplication + mucosal ablation	Regression of metaplasia
6	M	23	Adeno-carcinoma in high grade dysplasia	Long segment	PPI+ fundoplication + esophagectomy	No recurrence

BE = Barrett's Esophagus; CDLS = Cornelia de Lange Syndrome; PPI = Protonic Pump Inhibitors.

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American Journal of Medical Genetics Part A 146A:426–432 (2008)

Otitis Media With Effusion and Hearing Loss in Children With Cornelia de Lange Syndrome

Paola Marchisio,[1] Angelo Selicorni,[1] Lorenzo Pignataro,[2] Donatella Milani,[1] Elena Baggi,[1] Lara Lambertini,[1] Elisa Dusi,[1] Laura Villa,[3] Pasquale Capaccio,[2] Marta Cerutti,[1] Susanna Esposito,[1] and Nicola Principi[1]*

[1]Institute of Pediatrics, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy
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Audiological findings, genotype and clinical severity score in Cornelia de Lange syndrome

Paola Marchisio, Angelo Selicorni, Sonia Bianchini, Donatella Milani, Elena Baggi, Marta Cerutti, Lidia Larizza, Nicola Principi, Susanna Esposito

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Otolaryngological presentations of Cornelia de Lange syndrome

Jane Hamilton, W. Andrew Clement, Haytham Kubba

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Immunologic Features of Cornelia de Lange Syndrome

AUTHORS: Soma Jyonouchi, MD,[a,b] Jordan Orange, MD, PhD,[c] Kathleen E. Sullivan, MD, PhD,[a,b] Ian Krantz, MD,[b,d] and Matthew Deardorff, MD, PhD[b,d]

WHAT'S KNOWN ON THIS SUBJECT: Cornelia de Lange syndrome (CdLS) is a genetic syndrome with multisystem abnormalities. Infections are a significant cause of morbidity and mortality in

RESULTS: Recurrent infections were reported at high frequency in CdLS patients and included chronic ear infections (53%), chronic viral respiratory infections (46%), pneumonia (42%), sinus infections (33%), oral candidiasis (13%), sepsis (6%), and bacterial skin infections (4%). Full immune evaluation in 27 subjects led to identification of 9 cases of antibody deficiency syndrome in patients with severe forms of CdLS. Subjects with CdLS had decreased percentages of T regulatory cells and T follicular helper cells compared with normal control subjects ($P < .05$).

CONCLUSIONS: This study identified for the first time a high frequency of antibody deficiency in CdLS subjects, indicating a critical need for screening and management of immunodeficiency in CdLS patients with a history of well-documented severe or recurrent infections. Furthermore, our results indicate that impaired T-cell populations may be associated with antibody deficiency in CdLS. *Pediatrics* 2013;132:1–6

Orthopaedic manifestations of Brachmann–de Lange syndrome: a report of 34 patients

Andreas Roposch, Atul R. Bhaskar, Francis Lee, Sanya Adedapo, Maryline Mousny and Benjamin A. Alman

- Oltre alle possibili anomalie strutturali
- Contratture in flessione a livello di:

Gomiti (47%), ginocchia, anche

⇒Streching

- Problemi alla colonna (cifosi, scoliosi)
- Alluce valgo
- Piede equino-varo per aumento del tono del Tendine d'Achille

Orthopaedic manifestations of Brachmann–de Lange syndrome: a report of 34 patients

Andreas Roposch, Atul R. Bhaskar, Francis Lee, Sanya Adedapo, Maryline Mousny and Benjamin A. Alman

Non rara osservazione di necrosi avascolare dell'anca (Legg-Perthes disease like)

Sintomi

Dolore

e ipomobilità

Epilessia

- Incidenza: 23-26% dati letteratura, 24% dati personali
- Buona risposta a terapia farmacologica
- Frequente riscontro di anomalie EEG aspecifiche

Pediatric dental findings in CdLS

Conference report 2008

J.Hylton, R Mungo, R Lindemeyer, A. Kline, D Clemens

Valutazione diretta di 39 pz

Dati anamnestici raccolti dai genitori in 129 pz

<u>Osservazioni più frequenti:</u>

- Ritardata eruzione dentale
- Ritardata permuta dentale
- Necessità di ospedalizzazione/sedazione per il trattamento

Quale sarà il suo sviluppo psicomotorio ?

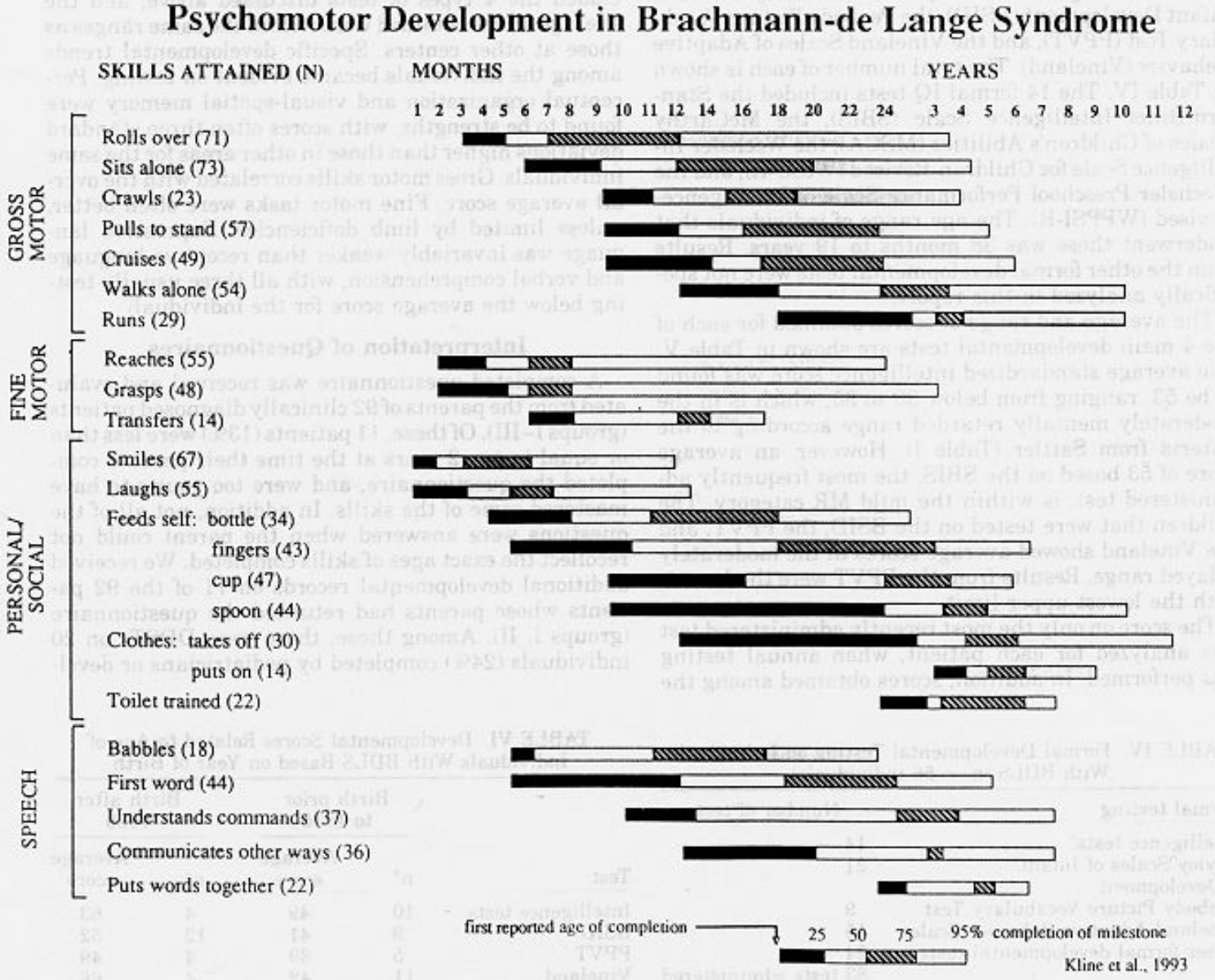

Fig. 1. Developmental chart for individuals with BDLS comparing ages of completion of milestones. Number of individuals on whom each range is based (n) is shown after each skill. (See text for explanation.)

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics
Neuropsychiatric Genetics

Communication, Cognitive Development and Behavior in Children With Cornelia de Lange Syndrome (CdLS): Preliminary Results

Paola Francesca Ajmone,[1] Claudia Rigamonti,[1] Francesca Dall'Ara,[1] Federico Monti,[1] Paola Vizziello,[1]* Donatella Milani,[2] Anna Cereda,[3] Angelo Selicorni,[3] and Antonella Costantino[1]

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Manuscript Received: 6 August 2013; Manuscript Accepted: 10 January 2014

Valutazione cognitiva

-17% (3 patients) normal IQ
-12% (2 patients) borderline IQ
-6% (1 patient) mild Intellectual Disability (ID)
-23% (4 patients) moderate ID
-12% (2 patients) profound ID

Competenze adattive

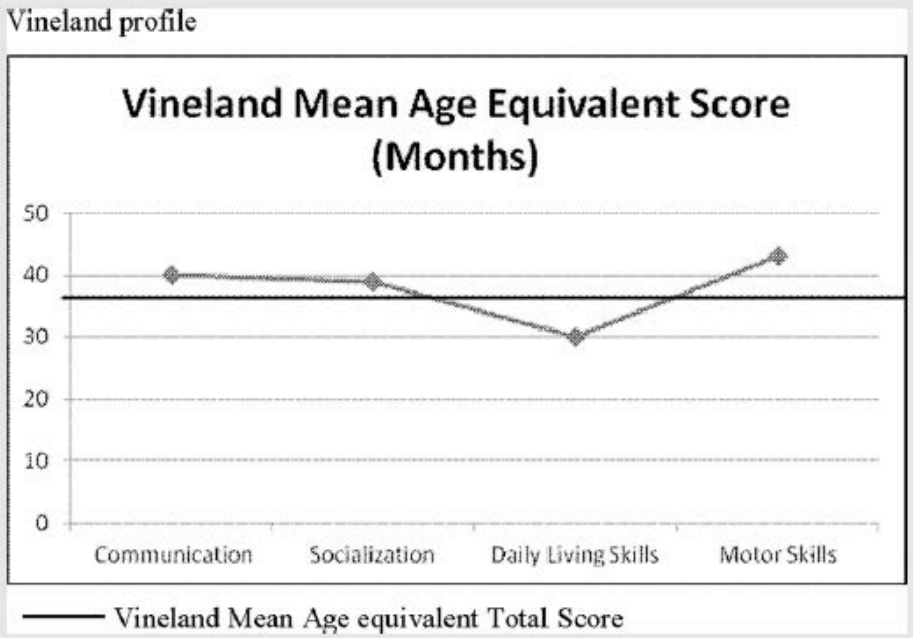


Fig. 1. Vineland means age equivalent total score.

Gap medio tra età cronologica ed età di sviluppo pari a 61 mesi

Area del linguaggio Classificazione (M.Goodbane)

- Talkers 3-4%
- Late talkers 30-40%

(prime parole entro 4-8 aa)

- Limited talkers 20-25%

(prime parole entro 7-10 aa)

- Non talkers 25-30%

Area linguaggio

TABLE I. Recep

Years at evaluation	MacArthur (receptive)	MacArthur (production)
2.5	2 years 5 months	1 year 3 months
3	10 months	<8 months
5.1	–	–
5.2	30 months	20 months
6.1	–	–
6.4	na	–
6.5	2 years	2 years
6.6	9 months	<8 months
7.1	–	–
8.1	na	na
9.6	–	–
9.8	–	–
11.2	11 months	<8 months
12.6	na	na
12.6	<17 months	<8 months
12.9	na	na
13.4	na	na

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *13: 58–69 (2007)*

The State of Research and Practice in Augmentative and Alternative Communication for Children with Developmental/Intellectual Disabilities

Krista M. Wilkinson[1,*] and Shannon Hennig[2]

[1]Communication Sciences and Disorders, Emerson College, Boston, Massachusetts

[2]Easter Seals of Massachusetts, Worcester, Massachusetts

So far, only 23% (4) of the patients having an AAC intervention in our sample had a follow-up assessment and the limited number of subjects does not permit any significant conclusion.

Anyway, first results indicate that patients with an AAC intervention show:

a) better comprehension of vocabulary and morphosyntax

b) a larger expressive vocabulary

c) better attention skills

d) wider autonomy in daily living skills.

671

Journal of Intellectual Disability Research doi: 10.1111/j.1365-2788.2007.00977.x

VOLUME 51 PART 9 pp 671–681 SEPTEMBER 2007

The behavioural phenotype of Cornelia de Lange Syndrome: a study of 56 individuals

E. Basile,[1] L. Villa,[1] A. Selicorni[2] & M. Molteni[1]

1 *Department of Child Psychiatry 'Eugenio Medea', Scientific Institute Bosisio Parini (Lc), Italy*
2 *Clinical Genetics, Department of Pediatrics, Milan, Italy*

Results Our participants demonstrated some behavioural characteristics that are frequently associated with CdLS (hyperactivity, attention disorder, anxiety, compulsive disorders, self-injurious behaviour and autistic-like features). Our findings demon-

Comportamenti autistici

TABLE II. CARS Score, ID, and Receptive Language

Years at evaluation	Receptive language (indirect/direct* evaluation)	Level of autistic behaviour (CARS)	ID classification using ICD-10
2.5	2 years 5 months	Non autistic	Normal IQ
3	10 months	Mild	Severe ID
5.1	3 year 8months	Mild	Mild ID
5.2	30 months	Mild	Moderate ID
6.1	1 year 6months	Severe	Not testable
6.4	4 years 6 months	Non autistic	Moderate ID
6.5	3 years	Mild	Borderline IQ
6.6	9 months*	Severe	Not testable
7.1	1 years 6 months	Severe	Profound
8.1	6 years	Non autistic	Borderline
9.6	1 year 6 months	Severe	Not testable
9.8	1 year 6 months	Non autistic	Not testable
11.2	11 months	Severe	Not testable
12.6	5.6 years	Non autistic	Normal IQ
12.6	<17 months	Severe	Moderate ID
12.9	5 years	Borderline	Moderate ID
13.4	5 years	Non autistic	Normal IQ

Finally, inagreement to previous data [Basile et al., 2007; Oliver et al., 2008],we observed a greater severity of autistic behaviors in the subjects with severe intellectual impairment.

Che vita avrà da grande ?

Fenotipo Lieve

Van Allen et al 1993

Sviluppo PM borderline o ritardo lieve

Ritardo di accrescimento meno marcato

Assenza o minor gravità delle malformazioni maggiori

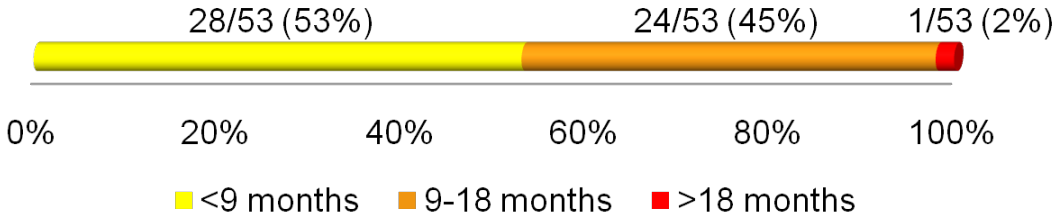
Liu and Krantz 2008

prevalence of mild phenotype 20-30%

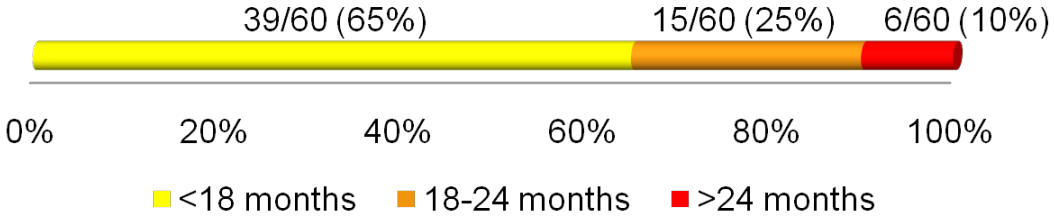
Studio pazienti mild (66pz)

Acquisizione normale o lievemente ritardata delle prime tappe motorie

Posizione seduta media 10 mesi



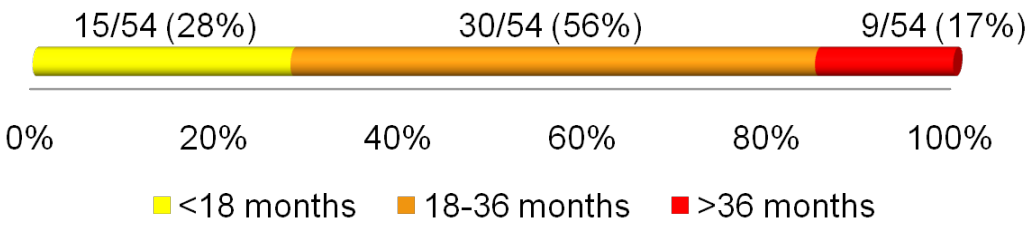
Primi passi media 19 mesi



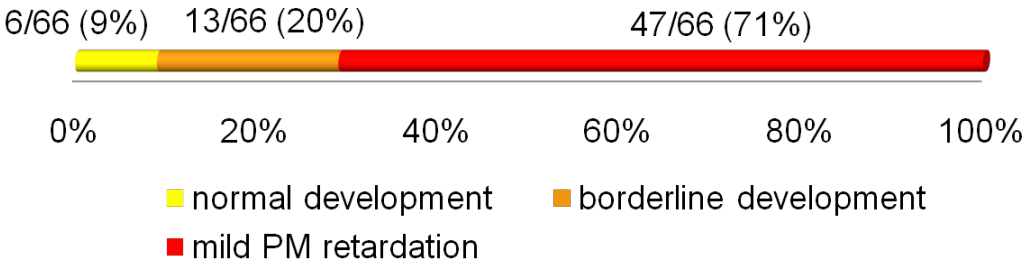
Studio pazienti mild (66pz)

Tutti I pazienti hanno acquisito la comunicazione verbale

Prime parole media 29 mesi



Livello di sviluppo psicomotorio/ intellettivo



CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics

Clinical Problems and Everyday Abilities of a Group of Italian Adolescent and Young Adults With Cornelia de Lange Syndrome

Giovanna Olioso,[1] Alice Passarini,[2] Francesca Atzeri,[2] Donatella Milani,[2] Anna Cereda,[2] Marta Cerutti, Silvia Maitz,[2] Francesca Menni,[2] and Angelo Selicorni[2]*

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Received 11 February 2009; Accepted 27 July 2009

TABLE IV. Personal Autonomies

	Ability absent	Partial achieved ability	Ability present
Self-washing	22 (49%)	18 (40%)	5 (11%)
Using bathroom	15 (33.3%)	18 (40%)	12 (26.75%)
Self-dressing and undressing	19 (42.2%)	16 (35.6%)	10 (22.2%)
Self-feeding	8 (17.8%)	9 (20%)	28 (62.2%)
Caring about their own objects	18 (40%)	13 (28.9%)	14 (31.1%)
Acceptable behavior at table	3 (6.7%)	25 (55.5%)	17 (37.8%)
Respecting social rules	17 (37.8%)	18 (40%)	10 (22.2%)
Taking part to group activities	10 (22.2%)	25 (55.6%)	10 (22.2%)

TABLE VI. Basic Linguistic Knowledge and Social Skills

	Yes	No
Knowing own age	14 (31%)	31 (69%)
Knowing town's name	21 (47%)	24 (53%)
Telling time	7 (16%)	38 (84%)
Understanding value of money	3 (7%)	42 (93%)
Able to call for help	34 (76%)	11 (24%)
Able to express wishes	26 (58%)	19 (42%)
Able to move independently into his house	40 (89%)	5 (11%)
Able to move within the city	11 (24%)	34 (76%)

Quali controlli deve fare mio figlio che ha la de Lange ?

Quando ?

Tabella IV *Follow up* pediatrico consigliato

Età (anni)	Frequenza dei controlli pediatrici
0-2	Trimestrale
2-4	Semestrale
4-6	Annuale
6-12	Biennale
>12	Triennale

Cosa fare ?

Tabella V Valutazioni di *follow up* consigliate

Da effettuarsi almeno una volta all'anno fino ai 6 anni e ogni 2-3 anni dopo i 6 anni

- Valutazione pediatrica generale
- Valutazione auxologica
- Valutazione neuropsichiatrica infantile (almeno annuale anche dopo i 6 anni)
- Valutazione gastroenterologica pediatrica +/- chirurgica pediatrica in caso di posizionamento di gastrostomia
- Valutazione cardiologica (biennale in assenza di cardiopatia congenita)
- Valutazione oculistica
- Valutazione odontoiatrica
- Valutazione ortopedica
- Esami ematochimici (emocromo+F, reticolociti, sideremia, transferrinemia, ferritinemia, funzionalità renale, metabolismo Ca/P, esami nutrizionali (soprattutto nei primi anni di vita), esame urine, sangue occulto fecale

Il mio pediatra non conosce questa sindrome. Mi devo fidare di lui ?

Cosa offrire al pediatra di famiglia

- La propria fiducia
- Il tempo di crescere con voi
- Materiale divulgativo/scientifico validato da associazione
- Aggiornamento costante delle vicende medico assistenziali del figlio

Cosa chiedere al pediatra di famiglia

- <u>Disponibilità</u>

- all'aggiornamento sulla specifica condizione
- all'ascolto delle preoccupazioni / dubbi, medici e non, che nascono e nasceranno
- al supporto concreto nei contatti con le realtà medico sociali (centro di eccellenza in primis)

Cosa chiedere al pediatra di famiglia

- <u>Assunzione di responsabilità riguardo alla</u>

- evoluzione auxologica (curve di crescita, prima valutazione nutrizionale)
- prevenzione pediatrica generale (vaccinazioni)
- funzione diagnostico terapeutica o, almeno, di "filtro ragionato" riguardo le problematiche mediche intercorrenti

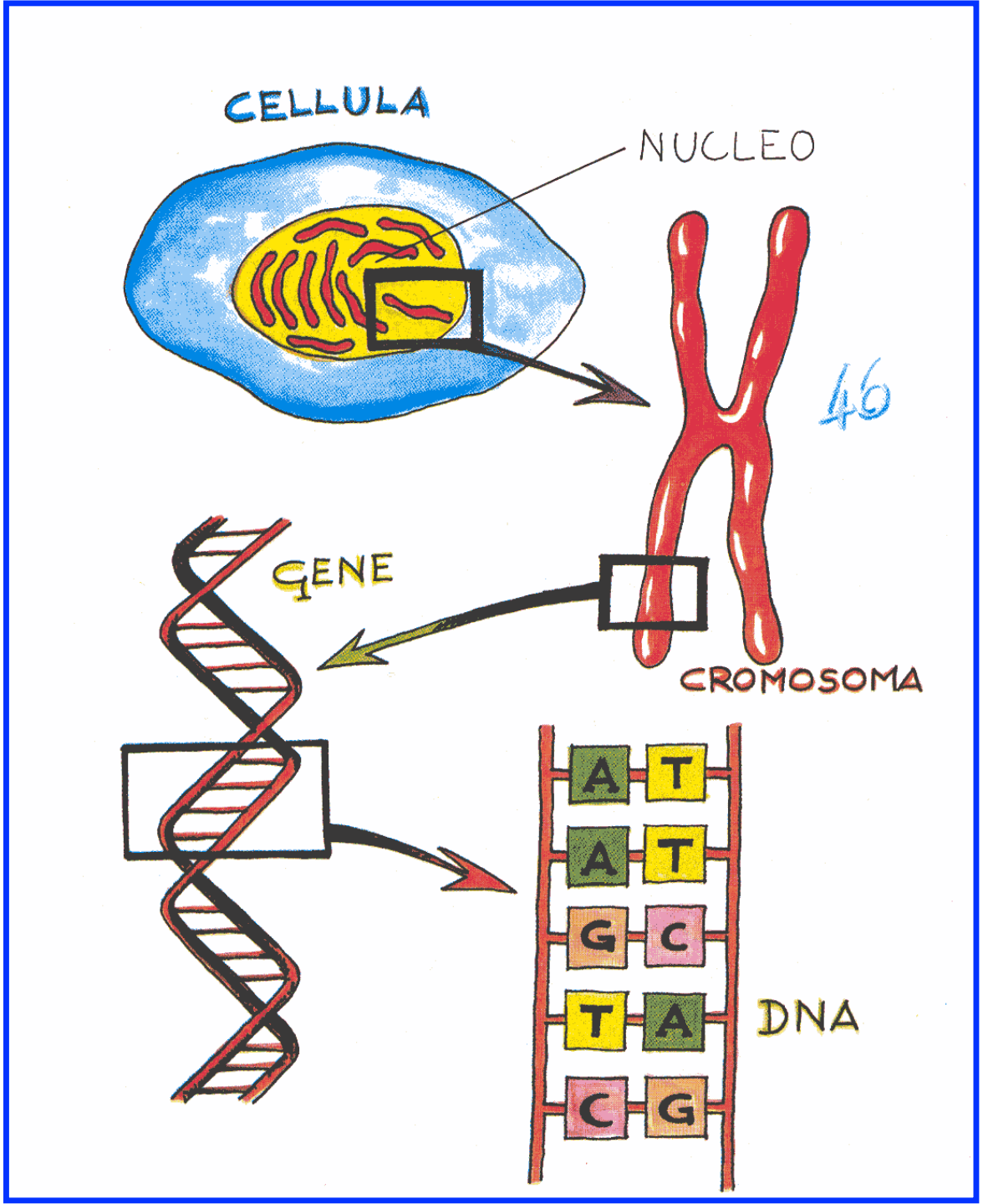
Cosa chiedere al pediatra di famiglia

- <u>Apertura e collaborazione nella gestione dei problemi trasversali</u>

- Problemi gastro enterologici (RGE, Stipsi)
- Problemi nutrizionali (PEG, Sondino NG)

…. Ove serva, in appoggio ai centri di riferimento

La de Lange è una malattia genetica ereditaria ?


CELLULA
NUCLEO
46
CROMOSOMA
GENE
A T
A T
G C
T A
C G
DNA

NIPBL
(50-55%)

SMC1L1
(5%)

SMC3
1 pts

Phenocopies
? %

Recenti scoperte

ARTICLE

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HDAC8 mutations in Cornelia de Lange Syndrome affect the cohesin acetylation cycle

Matthew A. Deardorff[1,2,*], **Masashige Bando**[3,*], **Ryuichiro Nakato**[3,*], **Erwan Watrin**[4,*], **Takehiko Itoh**[5], **Masashi Minamino**[3], **Katsuya Saitoh**[3], **Makiko Komata**[3], **Yuki Katou**[3], **Dinah Clark**[1], **Kathryn E. Cole**[6], **Elfride De Baere**[7], **Christophe Decroos**[6], **Nataliya Di Donato**[8], **Sarah Ernst**[1], **Lauren J. Francey**[1], **Yolanda Gyftodimou**[9], **Kyotaro Hirashima**[10], **Melanie Hullings**[1], **Yuuichi Ishikawa**[11], **Christian Jaulin**[4], **Maninder Kaur**[1], **Tohru Kiyono**[12], **Patrick M. Lombardi**[6], **Laura Magnaghi-Jaulin**[4], **Geert R. Mortier**[13], **Naohito Nozaki**[14], **Michael B. Petersen**[9,15], **Hiroyuki Seimiya**[8], **Victoria M. Siu**[16], **Yutaka Suzuki**[17], **Kentaro Takagaki**[18], **Jonathan J. Wilde**[1], **Patrick J. Willems**[19], **Claude Prigent**[4], **Gabriele Gillessen-Kaesbach**[20], **David W. Christianson**[6], **Frank J. Kaiser**[20], **Laird G. Jackson**[1,21], **Toru Hirota**[17], **Ian D. Krantz**[1,2], and **Katsuhiko Shirahige**[3,22]

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Short R

Somat
syndr
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mosaicism in
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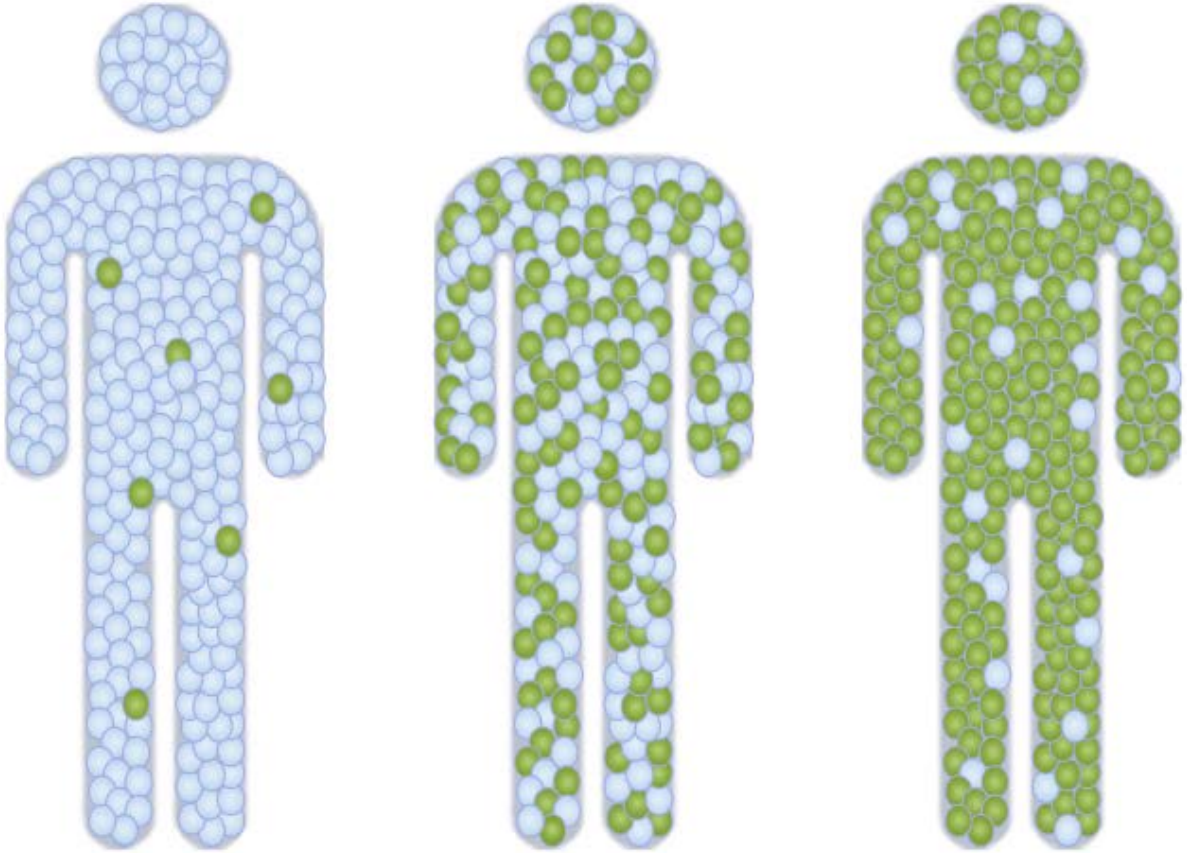
Cornelia de I

ini[a],
rni[b],
zza[a,f]



low-level mosaicism

1/2 abnormal cells

high-level mosaicism

abnormal karyotype
normal karyotype

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ORIGINAL ARTICLE

High rate of mosaicism in individuals with Cornelia de Lange syndrome

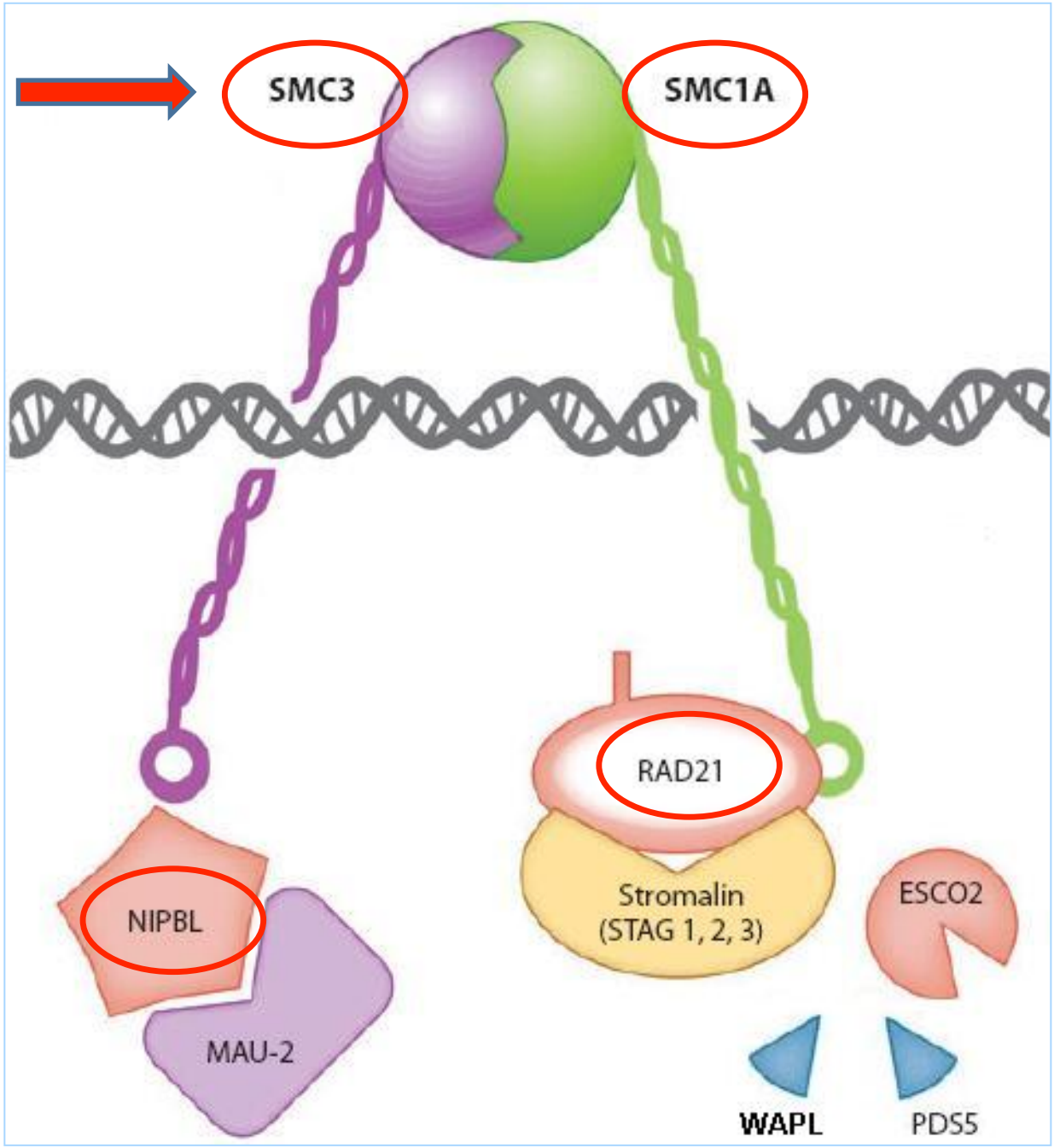
Sylvia A Huisman,[1,2] Egbert J W Redeker,[3] Saskia M Maas,[1,3] Marcel M Mannens,[3] Raoul C M Hennekam[1,3]

ABSTRACT

Background Cornelia de Lange syndrome (CdLS) is a well known malformation syndrome for which five causative genes are known, accounting for ~55–65% of cases. In this study, we hypothesised that mosaicism might explain some of the ~35–45% of cases without detectable mutation in DNA derived from lymphocytes; we investigated the frequency of *NIPBL* mutations in buccal cells in individuals negative for mutations in any of the five genes in lymphocytes; and we evaluated the efficiency of obtaining DNA from buccal swabs and the best strategy for optimal mutation detection in CdLS sequencing techniques failed to show pathogenic variants in CdLS individuals in whom mutations in the five known pathogenic CdLS genes had already been excluded (unpublished data). We hypothesised that this was caused by mosaicism and that searching for mutations using other tissues might yield additional mutations in genes known to cause CdLS.

We describe here the results of *NIPBL* mutation analysis in buccal cells in CdLS individuals without a detectable mutation in one of the five known genes in lymphocytes. Furthermore, we report on the efficiency of molecular analysis of buccal swabs

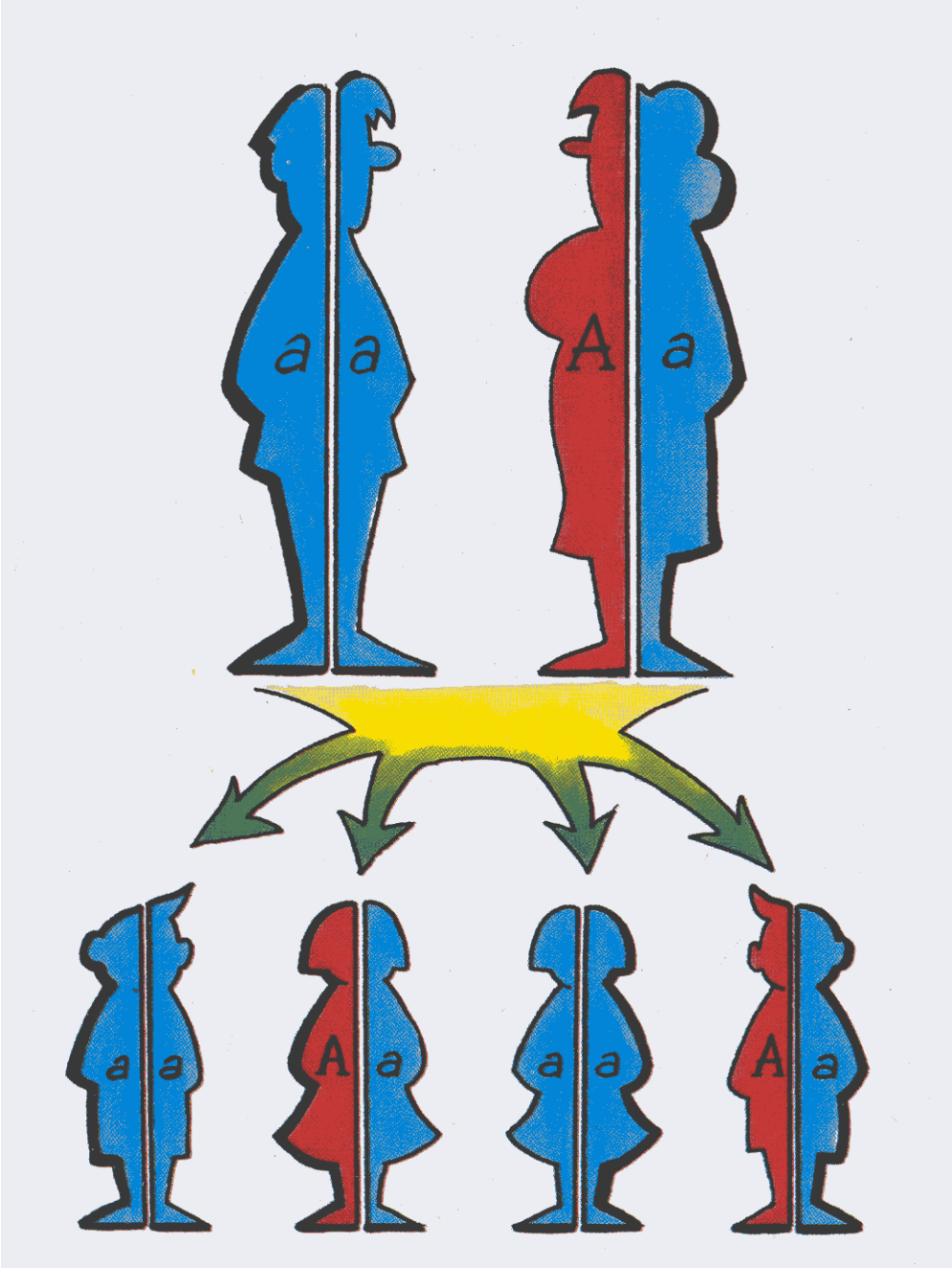
HDAC8


SMC3
SMC1A
RAD21
Stromalin
(STAG 1, 2, 3)
ESCO2
NIPBL
MAU-2
WAPL
PDS5

Se avremo altri figli avranno ancora la de Lange ? E i figli dei nostri figli ?

Malattia autosomica Dominante

NIPBL, RAD21, SMC3



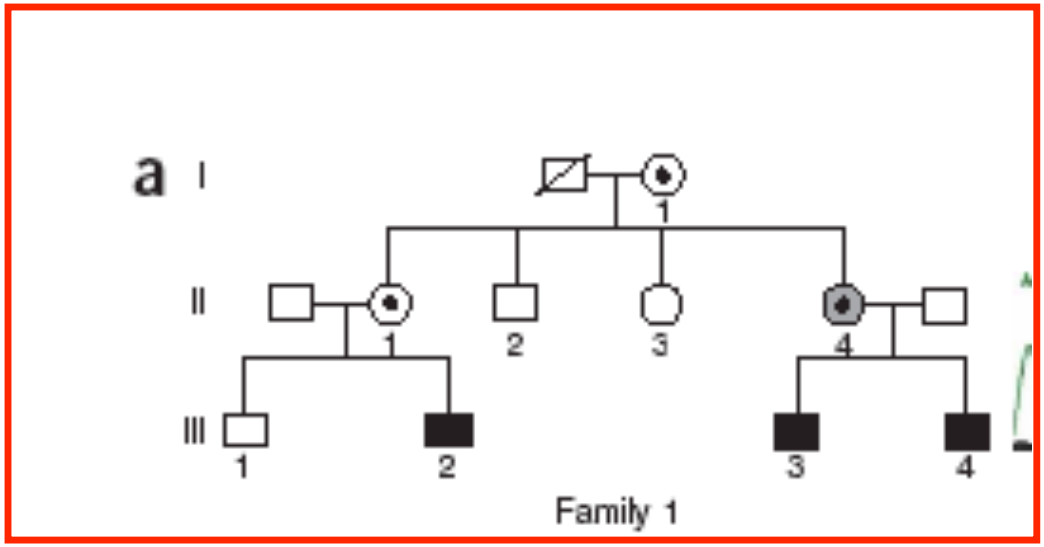
Rischio di ricorrenza

- Se una copia del gene è alterata si ha la comparsa dei segni della sindrome
- Solitamente chi non ha segni riferibili alla sindrome non ha nemmeno anomalie del gene
- Nella maggioranza dei pazienti la mutazione insorge casualmente nel DNA di chi ha la sindrome

Rischio di ricorrenza

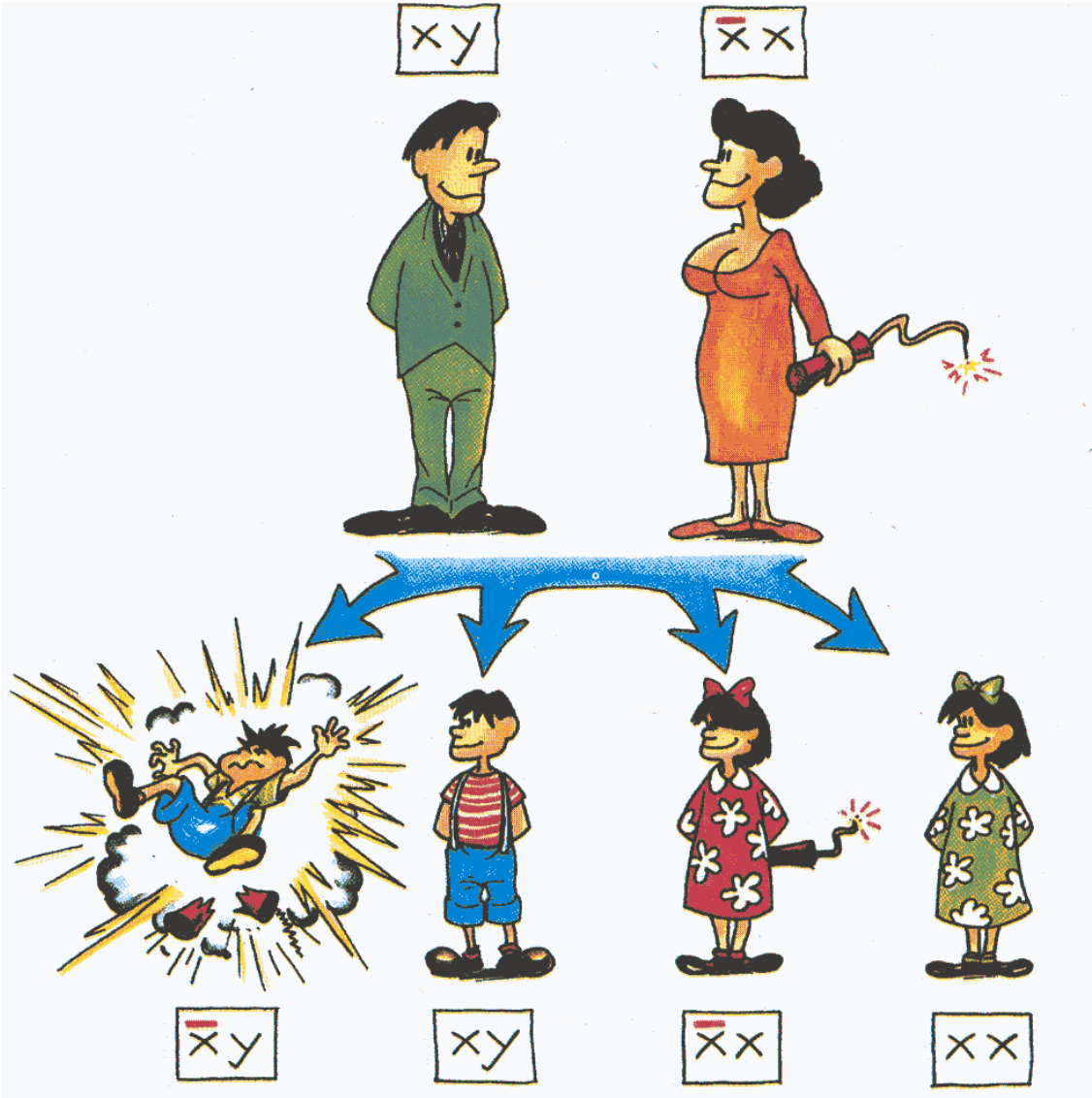
- La situazione può essere diversa per i geni localizzati sul cromosoma X

SMC1A/HDAC8 !!!!



Malattia recessive legate all'X

SMC1A
HDAC8



CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Germline Mosaicism in Cornelia de Lange Syndrome

Thomas P. Slavin,[1]* Noam Lazebnik,[1,2] Dinah M. Clark,[3] Jaime Vengoechea,[1] Leslie Cohen,[1] Maninder Kaur,[3] Laura Konczal,[1] Carol A. Crowe,[4] Jane E. Corteville,[1,2] Malgorzata J. Nowaczyk,[5] Janice L. Byrne,[6] Laird G. Jackson,[7] and Ian D. Krantz[3,8]

Suspected or confirmed cases of germline mosaicism in our database range from a conservative 3.4% up to 5.4% of our total cohort. In conclusion, the potential reproductive recurrence risk due to germline mosiacism should be addressed in prenatal counseling for all families who have had a previously affected pregnancy or child with CdLS. © 2012 Wiley Periodicals, Inc.

CORRESPONDENCE

AMERICAN JOURNAL OF medical genetics PART A

Germline Mosaicism in Cornelia de Lange Syndrome: Dilemmas and Risk Figures

Milena Mariani,[1] Laura R. Bettini,[1] Anna Cereda,[1] Silvia Maitz,[1] Cristina Gervasini,[2] Silvia Russo,[3] Maura Masciadri,[3] Andrea Biondi,[1] Lidia Larizza,[2,3] and Angelo Selicorni[1]*

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We evaluated 158 patients clinically diagnosed with CdLS according to international criteria [Kline et al., 2007]. We collected a family history for all patients and directly evaluated the parents and siblings. In one additional family with two male siblings and an affected first cousin, segregation of a *SMC1A* mutation in the mildly affected mother and her sister was demonstrated [Musio et al., 2006]. The other 158 parental couples were considered unaffected upon clinical evaluation. In our cohort, 92 families had additional children, for a total of 125 siblings; none showed clinical signs of possible CdLS, not even very mildly expressed.

Nel caso di fratelli/ sorelle, zii/zie, cugini/cugine sane della persona con de Lange ?

- Se le analisi dimostrano che nei genitori la mutazione del gene malattia è assente => rischio identico alla popolazione generale
- Se i test genetici risultano tutti nella norma ed i genitori sono sani => rischio probabilmente uguale alla popolazione generale
- Se la mamma è portatrice sana di una mutazione di uno dei due geni localizzati sul cromosoma X => attenzione al suo ceppo familiare => estensione della analisi agli altri soggetti

In che cosa ci aiuta la genetica ?

Utilità della caratterizzazione genetica

- Definizione di una certezza diagnostica
- Stima del rischio di ricorrenza familiare
- Definizione della prognosi
- Terapia specifica

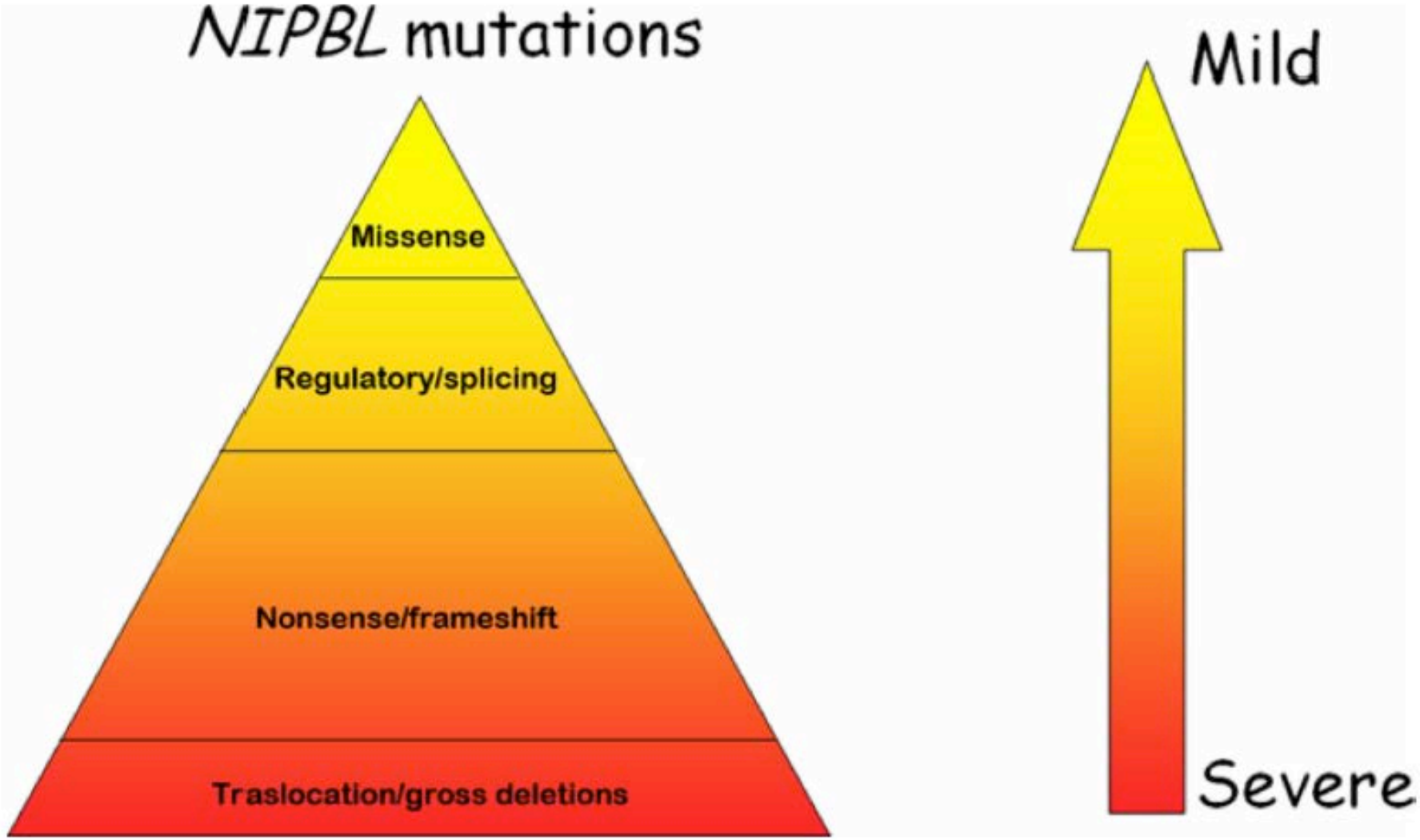

Figure 3.
Genotype–phenotype correlations in CdLS due to *NIPBL* mutations.

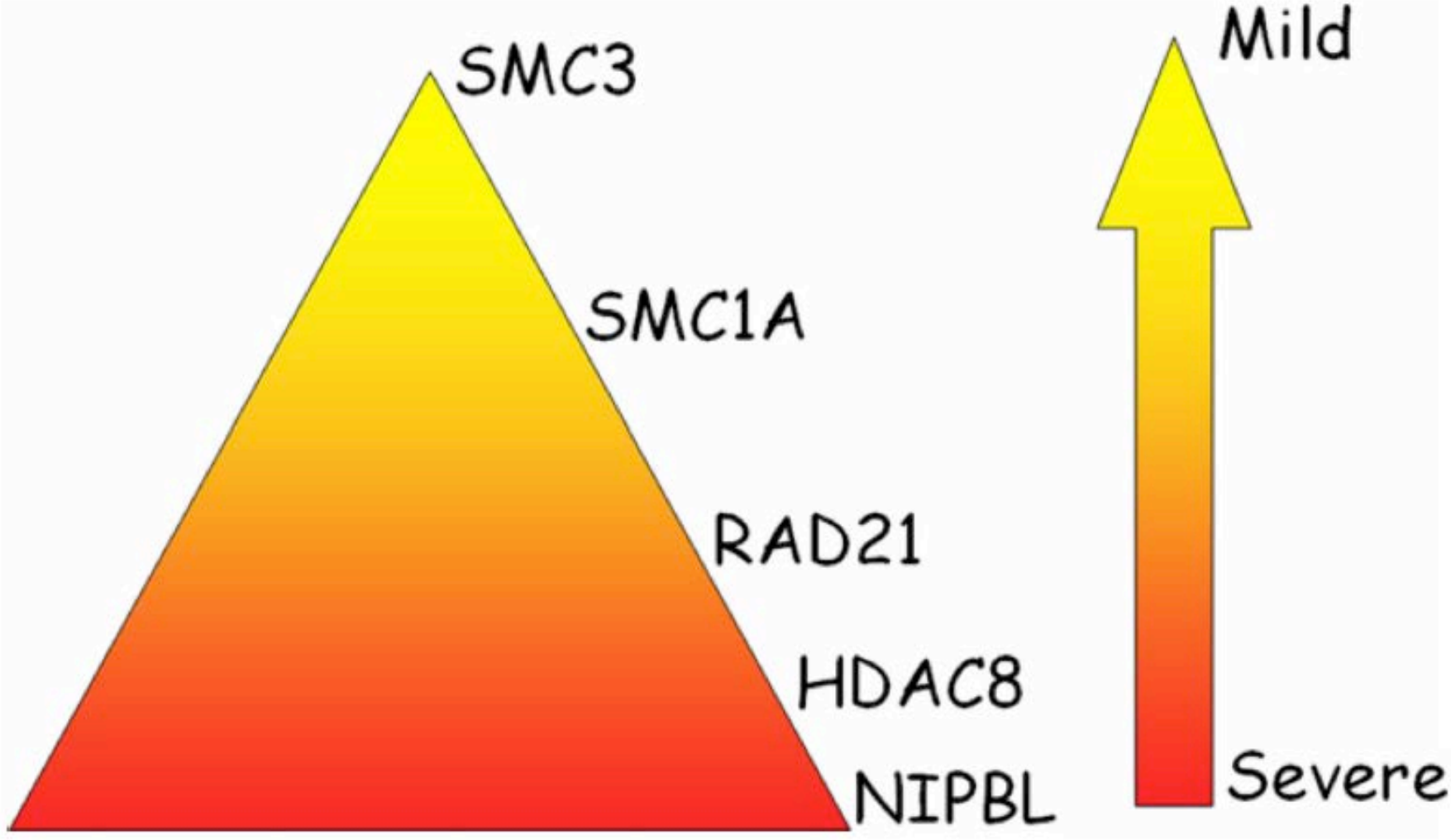

Figure 4.
Diagram representing the correlation genotype–phenotype of the five CdLS causative genes.

Ma la ricerca sta andando avanti ? Cosa ci possiamo aspettare ?

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«Se uno sogna da solo, è solo un sogno.
Se molti sognano insieme, è l'inizio di una nuova realtà»

Grazie per l'attenzione !!!