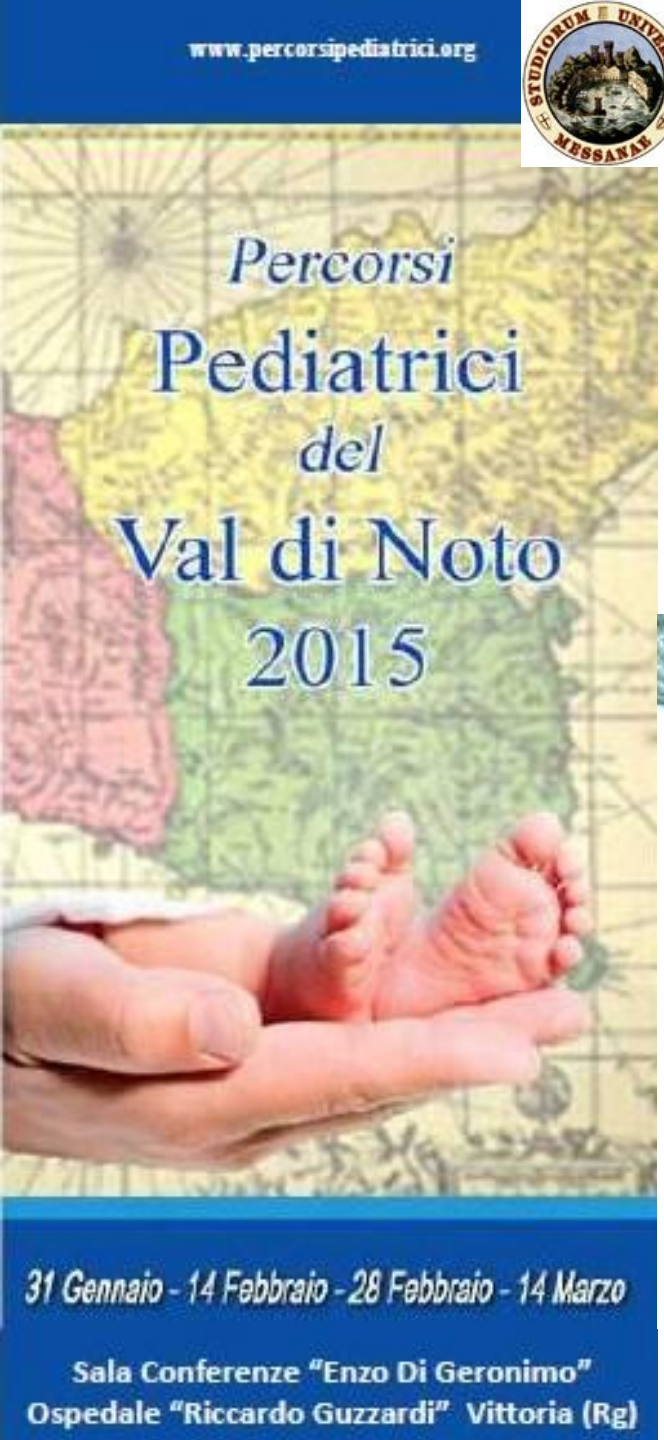


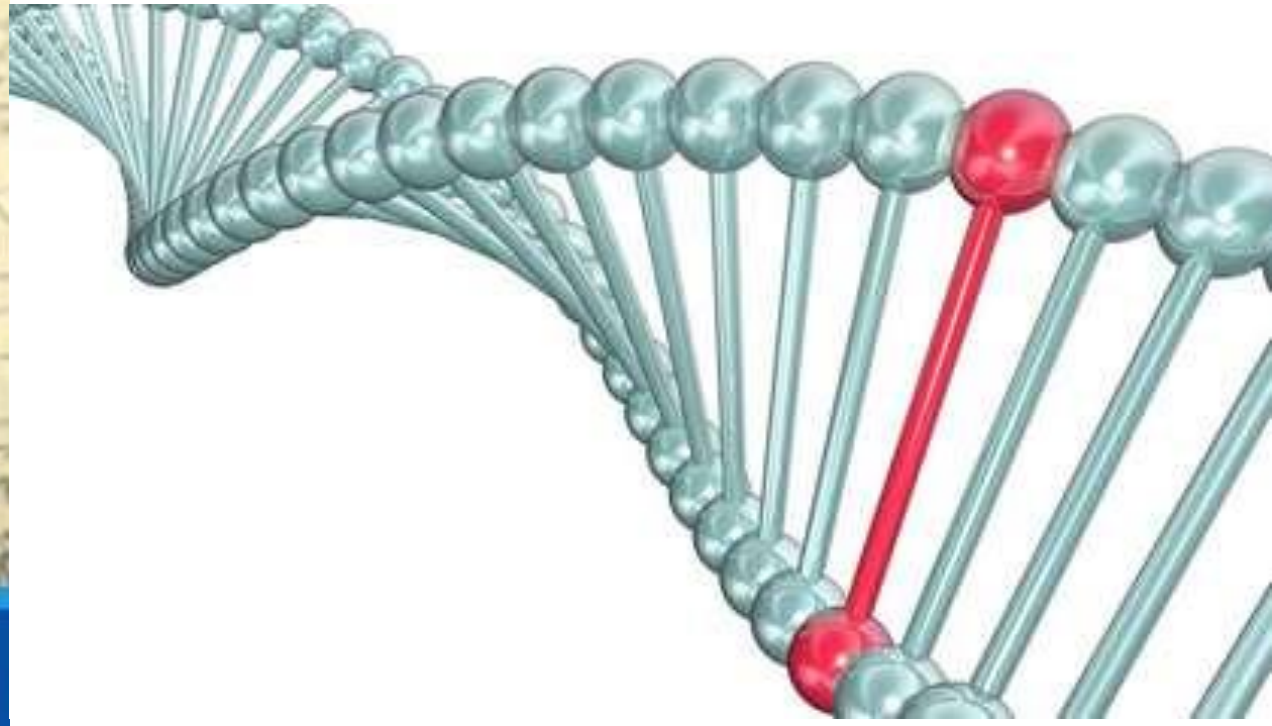
Università degli Studi di Messina

Dipartimento di Scienze Pediatriche, Ginecologiche, Microbiologiche e Biomediche

Unità Operativa Complessa di Genetica e Immunologia Pediatrica

Direttore: prof. Carmelo Salpietro

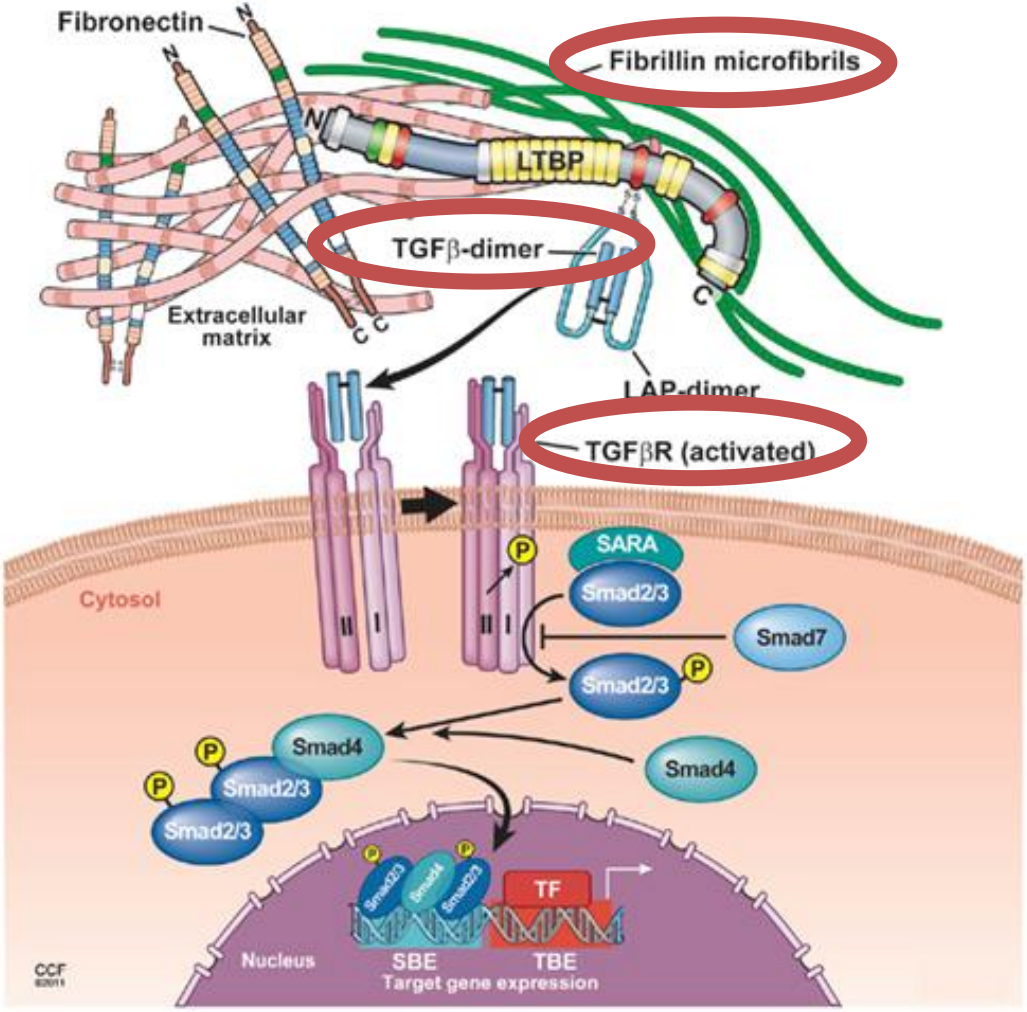
SINDROME DI MARFAN GENETICA



Vincenzo Procopio

•Proteina di matrice extracellulare
•Partecipa alla formazione delle microfibrille
•Formazione e omeostasi della matrice elastica, ancoraggio delle cellule , regolazione dei fattori di crescita.
•Interagisce con il growth factor TGFβ.

latent TGF-beta binding proteins

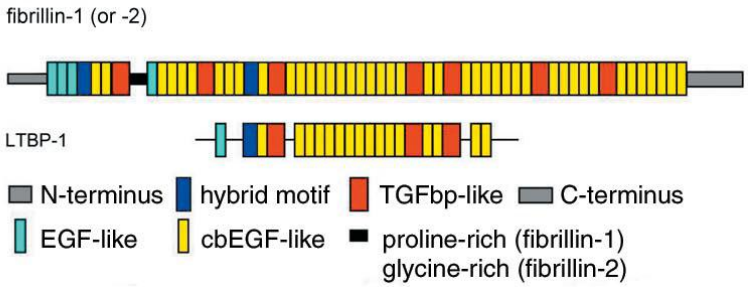


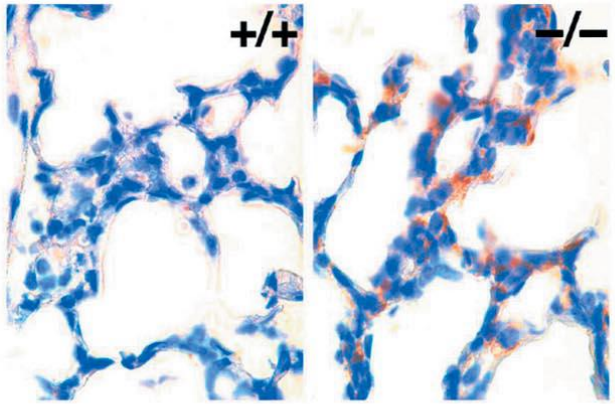
letter

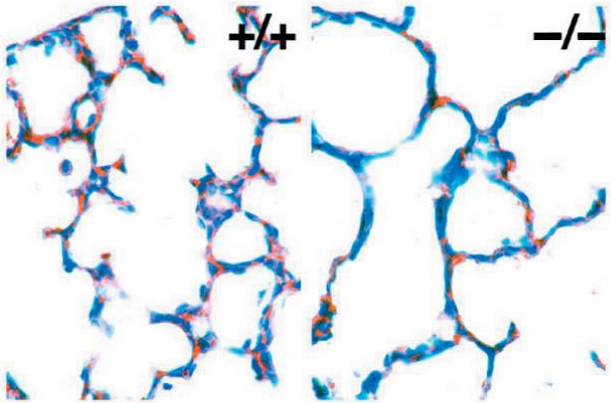
Dysregulation of TGF-β activation contributes to pathogenesis in Marfan syndrome

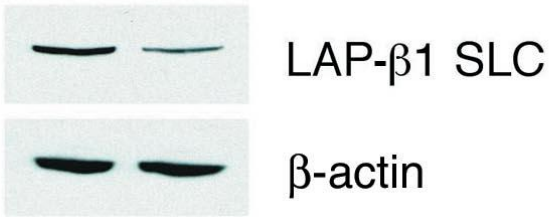
Enid R. Neptune[1,2], Pamela A. Frischmeyer[2], Dan E. Arking[2], Loretha Myers[2], Tracie E. Bunton[3], Barbara Gayraud[4], Francesco Ramirez[4], Lynn Y. Sakai[5] & Harry C. Dietz[2,6]

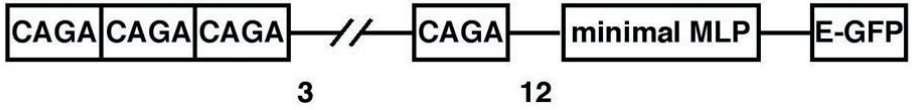
Published online 24 February 2003; doi:10.1038/ng1116

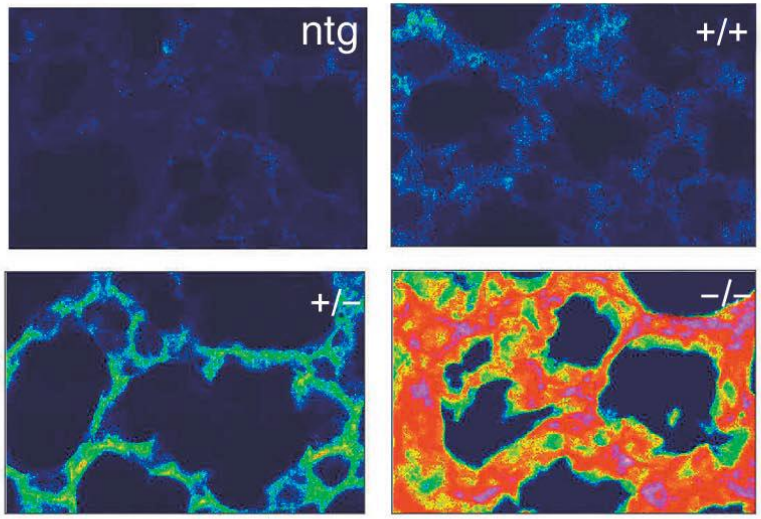

fibrillin-1 (or -2)
LTBP-1
N-terminus
hybrid motif
TGFbp-like
C-terminus
EGF-like
cbEGF-like
proline-rich (fibrillin-1)
glycine-rich (fibrillin-2)

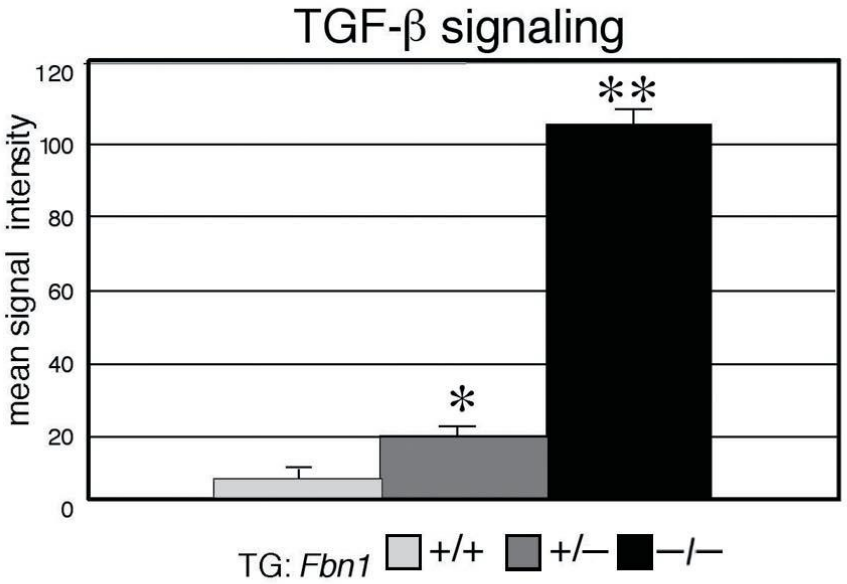

TGF-β
+/+
–/–


LAP-β1
+/+
–/–


LAP-β1 SLC
β-actin


CAGA
CAGA
CAGA
CAGA
minimal MLP
E-GFP
3
12


ntg
+/+
+/–
–/–

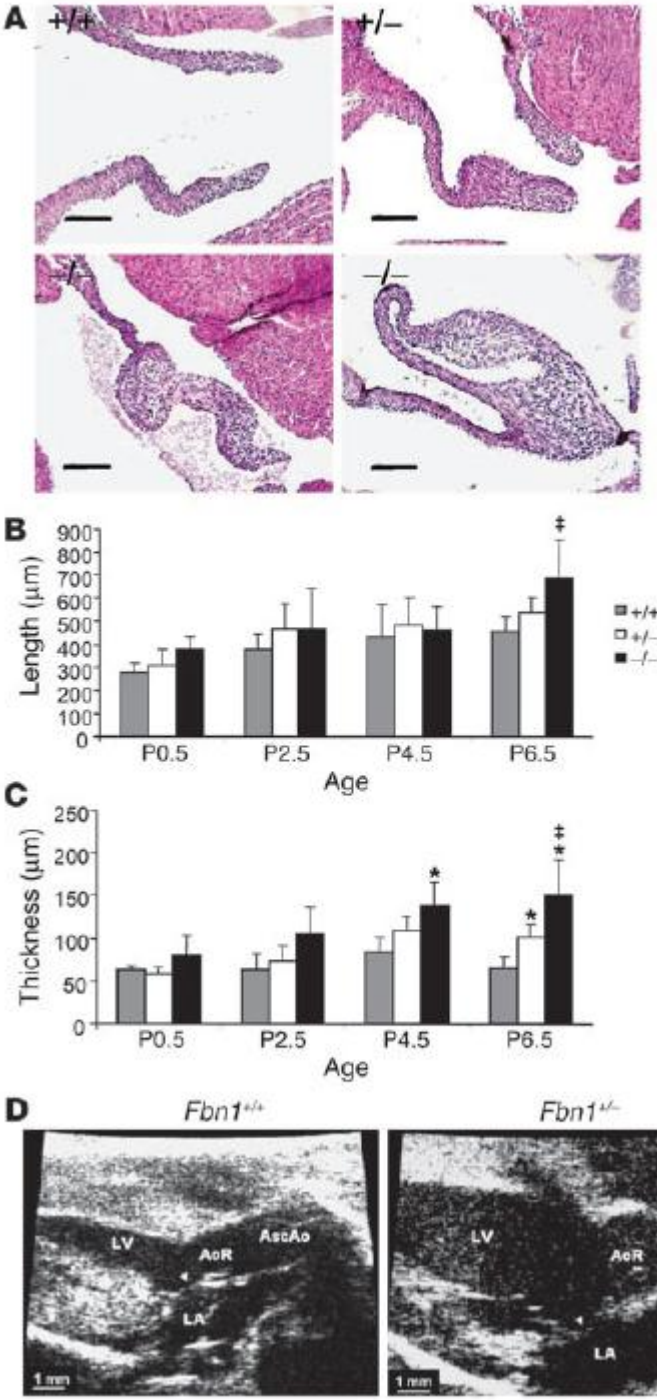

TGF-β signaling
mean signal intensity
120
100
80
60
40
20
0
*
**
TG: Fbn1
+/+
+/–
–/–

Research article Related Commentary, page 1543

TGF-β–dependent pathogenesis of mitral valve prolapse in a mouse model of Marfan syndrome

Connie M. Ng,[1] Alan Cheng,[2] Loretha A. Myers,[1] Francisco Martinez-Murillo,[3] Chunfa Jie,[1] Djahida Bedja,[4] Kathleen L. Gabrielson,[4] Jennifer M.W. Hausladen,[5] Robert P. Mecham,[5] Daniel P. Judge,[2] and Harry C. Dietz[1,2,3,6]

[1]McKusick-Nathans Institute of Genetic Medicine, [2]Department of Medicine, [3]Department of Molecular Biology and Genetics, and [4]Department of Comparative Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [5]Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri, USA. [6]Howard Hughes Medical Institute, Chevy Chase, Maryland, USA.



Spine (Phila Pa 1976). 2005 Feb 1;30(3):291-3.

Toward an understanding of dural ectasia: a light microscopy study in a murine model of Marfan syndrome.

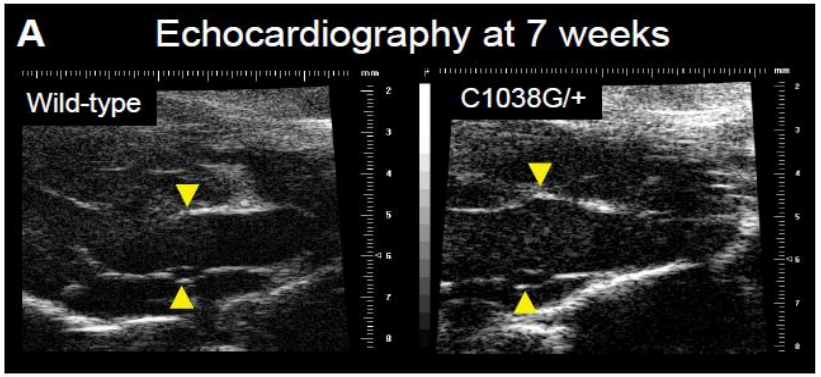
Jones KB[1], Myers L, Judge DP, Kirby PA, Dietz HC, Sponseller PD.
Department of Orthopaedic Surgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, USA. kevin-jones@uiowa.edu

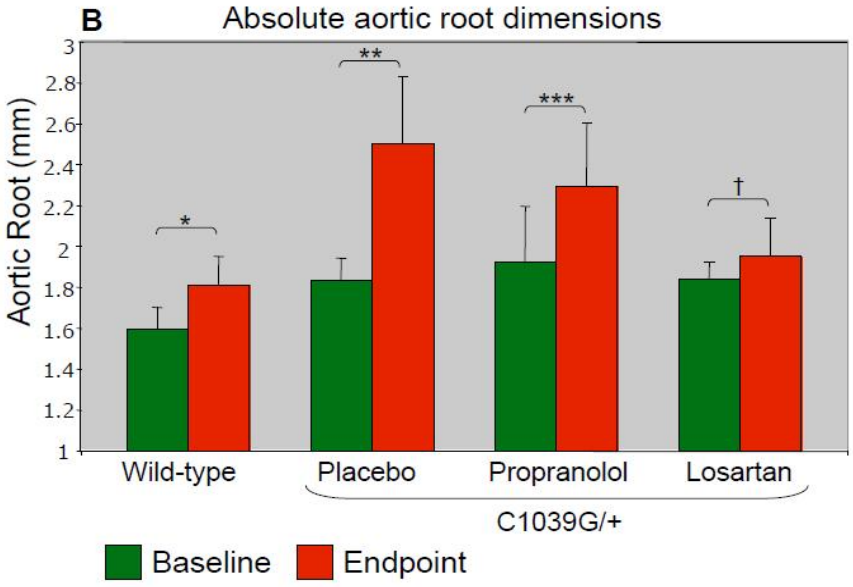
Published in final edited form as:
Science. 2006 April 7; 312(5770): 117–121.

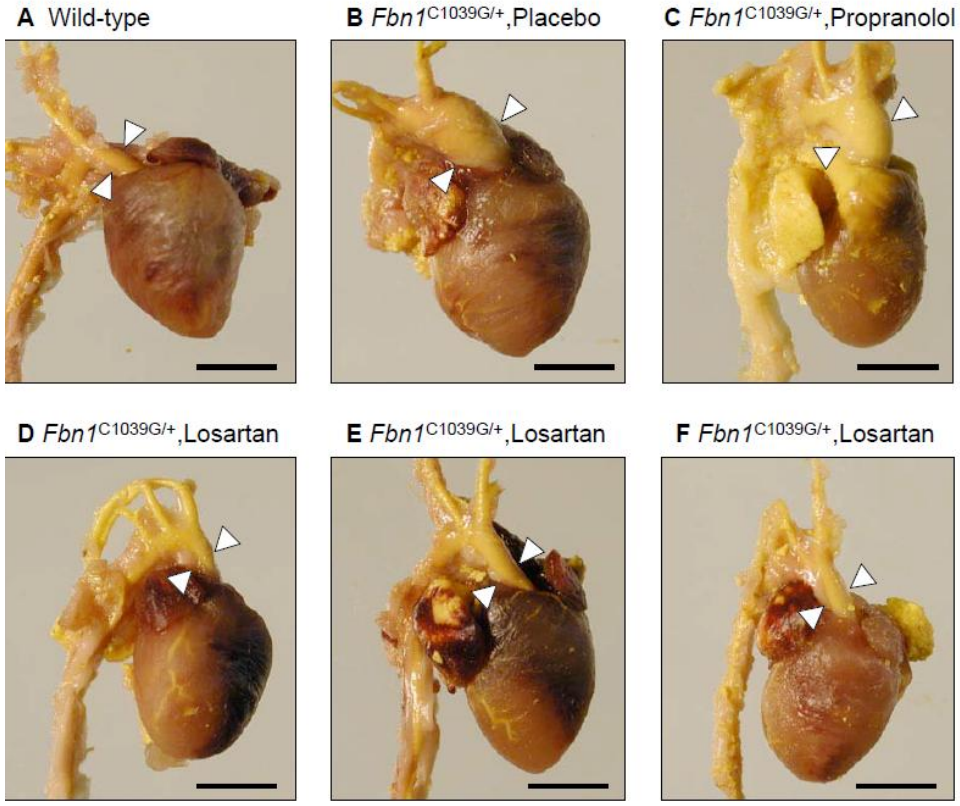
Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

Jennifer P. Habashi[1,*], Daniel P. Judge[2,*], Tammy M. Holm[1], Ronald D. Cohn[1], Bart L. Loeys[1], Timothy K. Cooper[1,3], Loretha Myers[1], Erin C. Klein[1], Guosheng Liu[3], Carla Calvi[2], Megan Podowski[2], Enid R. Neptune[2], Marc K. Halushka[4], Djahida Bedja[3], Kathleen Gabrielson[3], Daniel B. Rifkin[5], Luca Carta[6], Francesco Ramirez[6], David L. Huso[3], and Harry C. Dietz[1,2,†]

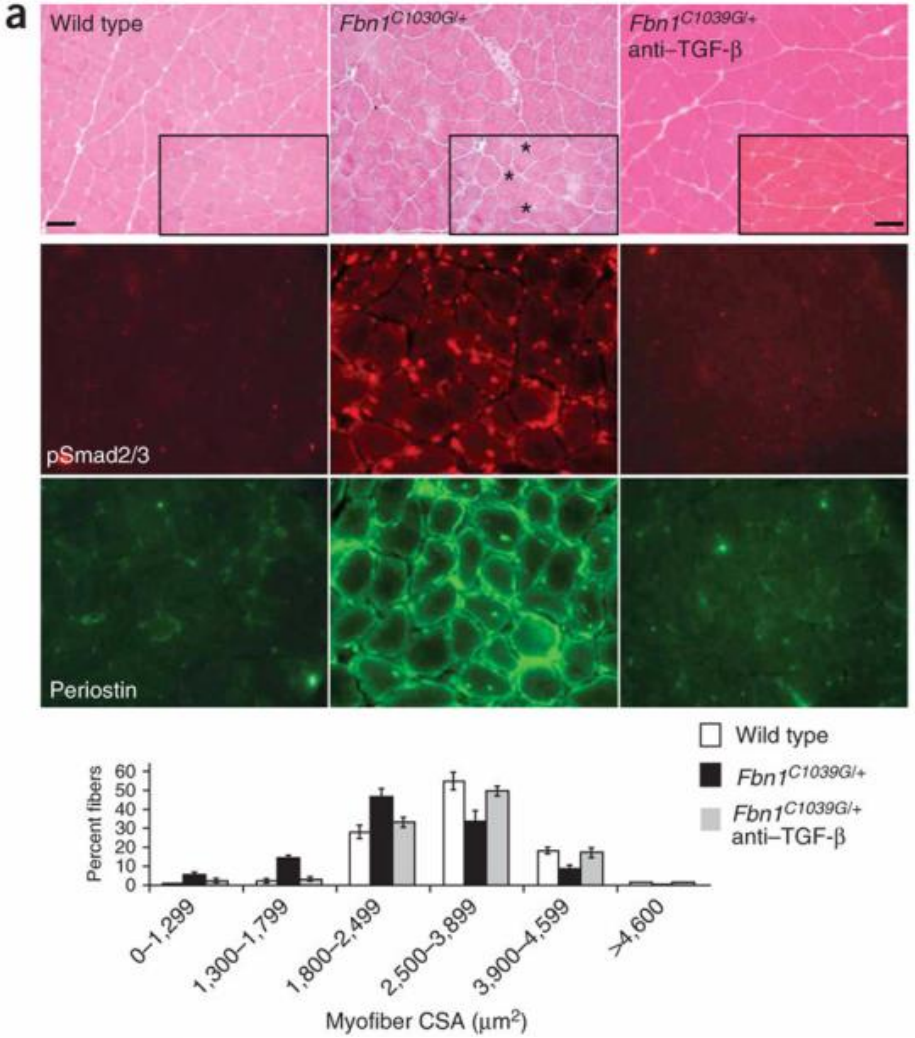
Antagonista TGF-β
TGF-β–neutralizing antibody o
angiotensin II type 1 receptor (AT1) blocker (losartan)

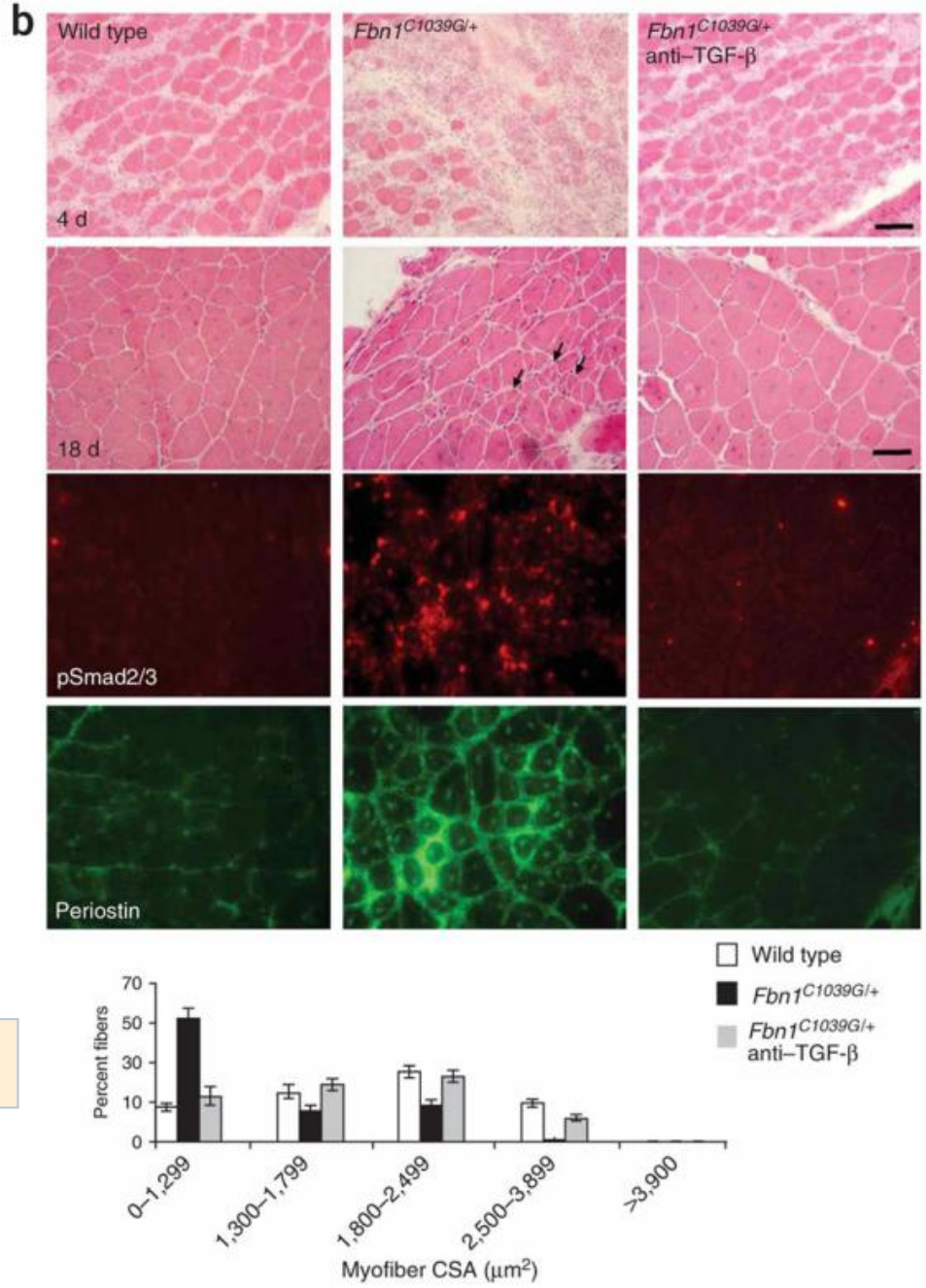






Scale bars (*A*-F), 4 mm.





Published in final edited form as:
Nat Med. 2007 February ; 13(2): 204–210. doi:10.1038/nm1536.

Angiotensin II type 1 receptor blockade attenuates TGF-β–induced failure of muscle regeneration in multiple myopathic states

Ronald D Cohn[1,2], **Christel van Erp**[1], **Jennifer P Habashi**[2,3], **Arshia A Soleimani**[1], **Erin C Klein**[1], **Matthew T Lisi**[1], **Matthew Gamradt**[1], **Colette M ap Rhys**[1,2], **Tammy M Holm**[1], **Bart L Loeys**[1], **Francesco Ramirez**[4], **Daniel P Judge**[5], **Christopher W Ward**[6], and **Harry C Dietz**[1,2]

[1] McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, 733 N Broadway, Baltimore, Maryland 21205, USA

Test genetici molecolari

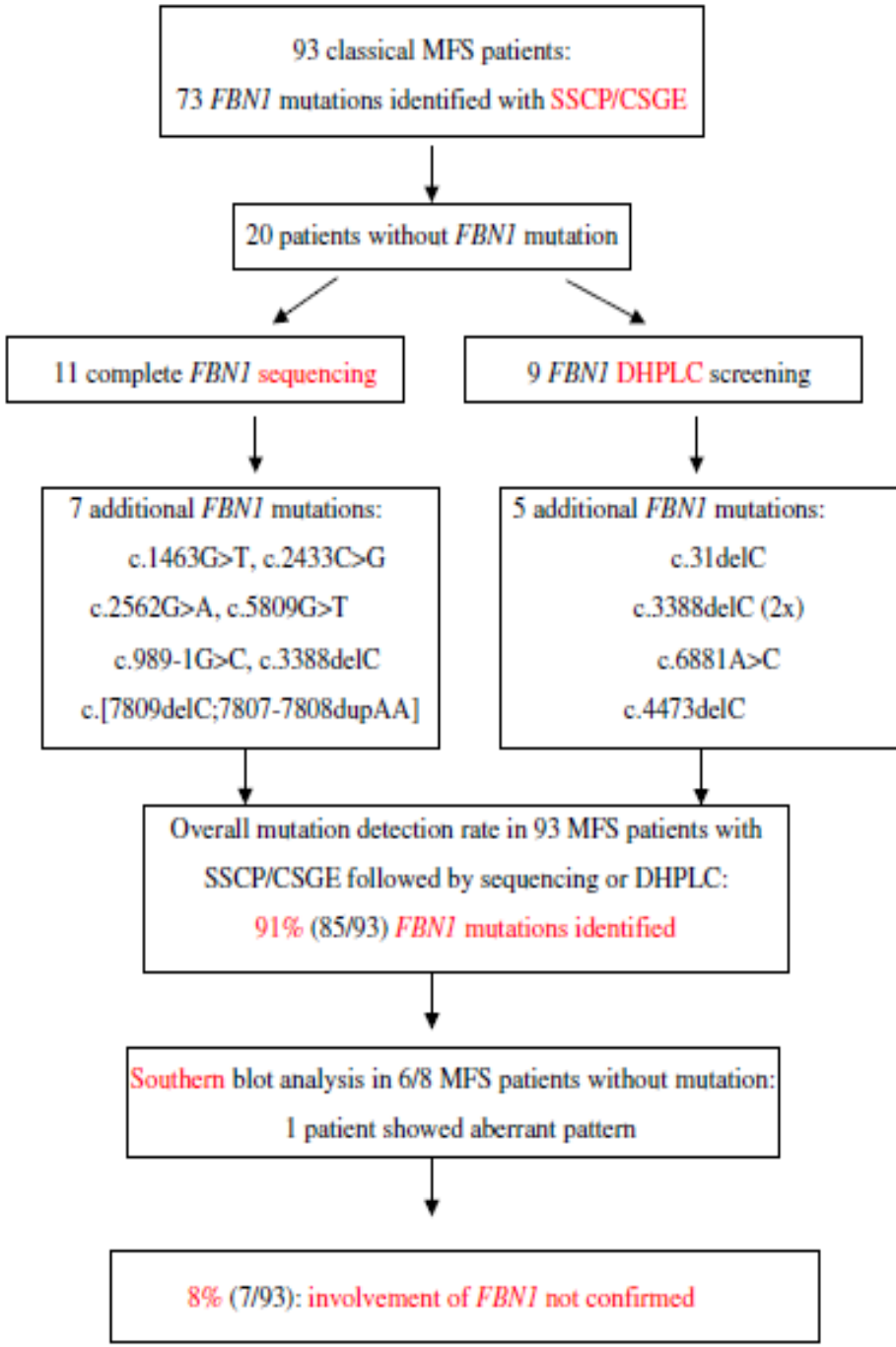
Gene.

FBN1 unico gene in cui le varianti patogenetiche sono associate alla sindrome di Marfan

Sensibilità incompleta - cause sconosciute

posizione di alcune varianti patogenetiche di alcuni pazienti (grandi delezioni o mutazioni nel promotore) ?

eterogeneità del locus (mutazioni in geni differenti che causano lo stesso fenotipo) ?



HUMAN MUTATION 24:140–146 (2004)

RESEARCH ARTICLE

Comprehensive Molecular Screening of the *FBN1* Gene Favors Locus Homogeneity of Classical Marfan Syndrome

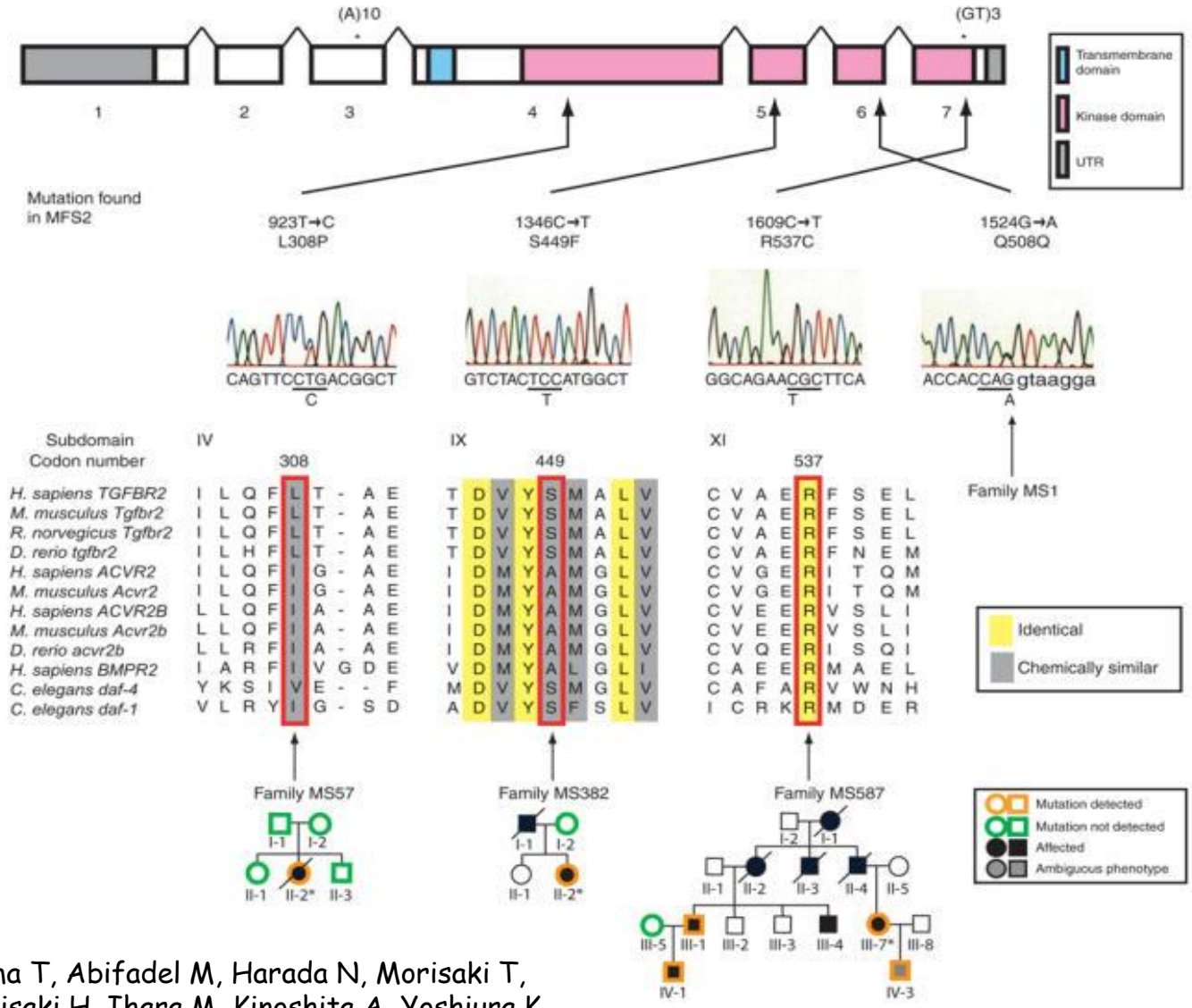
B. Loeys,[1] J. De Backer,[1] P. Van Acker,[1] K. Wettinck,[1] G. Pals,[2] L. Nuytinck,[1] P. Coucke,[1] and A. De Paepe[1*]

[1]*Ghent University Hospital, Center for Medical Genetics, Ghent, Belgium;* [2]*Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands*

ETEROGENEITÀ

Sindrome di Marfan di tipo 2

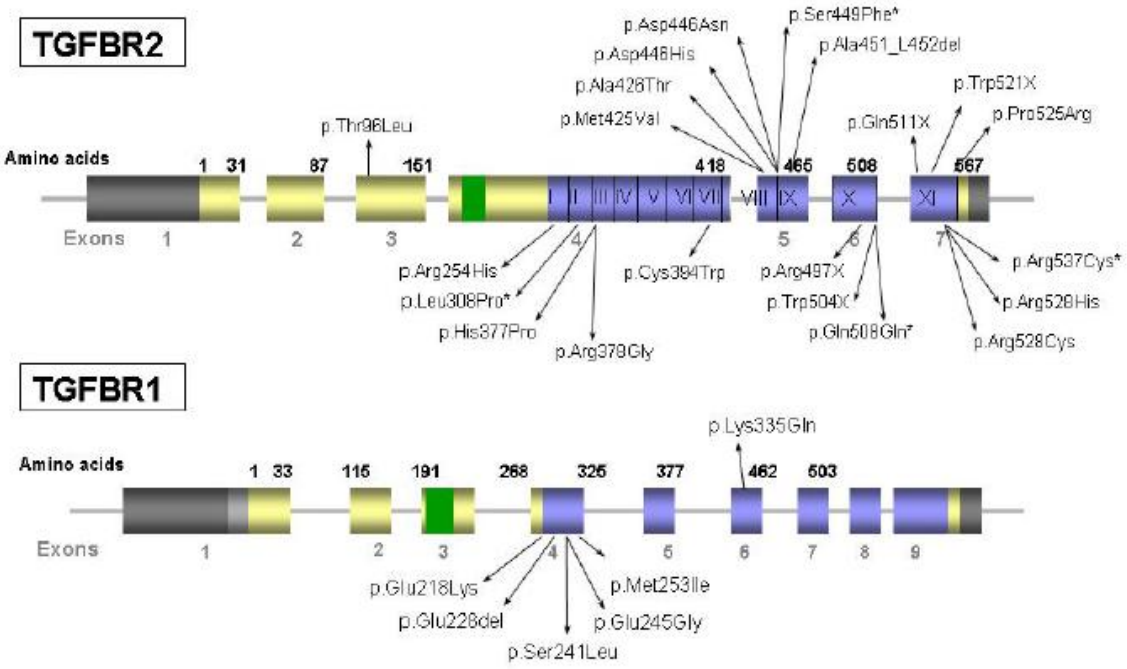
Mutazioni in *TGFBR2*
No ectopia lentis
No dolicostenomelia



Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N.
Heterozygous TGFBR2 mutations in Marfan syndrome.
Nat Genet. 2004;36:855–60.

Mutazioni in eterozigosi *TGFBR1* o *TGFBR2*
Sindrome di Loeys-Dietz
Alcuni segni clinici sovrapponibili

- aracnodattilia
- aneurisma dell'arco aortico
- deformità toraciche
- scoliosi
- ectasia durale



Nat Genet. 2005 Mar;37(3):275-81

A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2.

Loeys BL[1], Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC.

[1]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Mutazioni in *TGFBR2 e TGFBR1 in soggetti con diagnosi di sindrome di marfan classica*

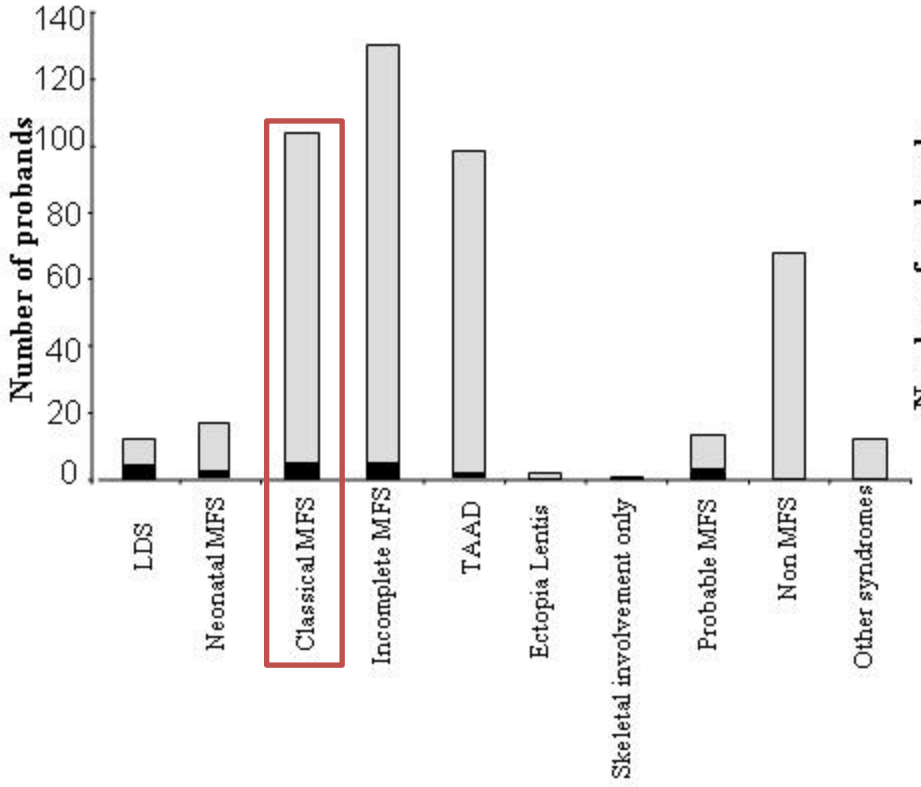
HUMAN MUTATION Mutation in Brief #1031, 29:E284–E295, (2008) Online

MUTATION IN BRIEF

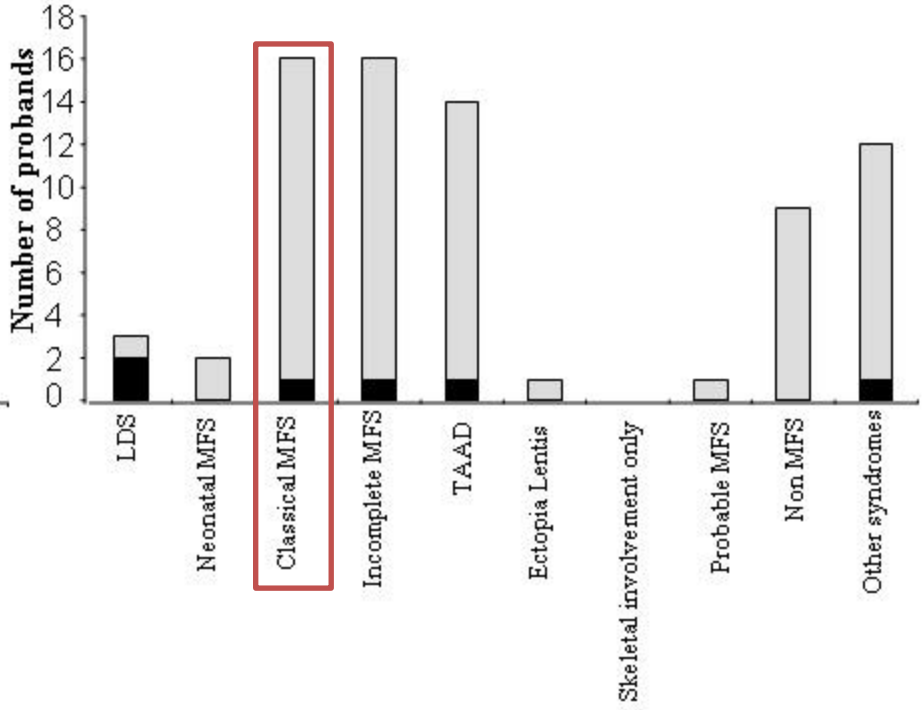
Identification of 23 *TGFBR2* and 6 *TGFBR1* Gene Mutations and Genotype-phenotype Investigations in 457 Patients with Marfan Syndrome Type I and II, Loeys-Dietz Syndrome and Related Disorders

Chantal Stheneur[1,2,3], Gwenaëlle Collod-Béroud[4,5], Laurence Faivre[6,7], Laurent Gouya[2,8,9,10], Gilles Sultan[2,11], Jean-Marie Le Parc[2,10,12], Bertrand Moura[2,12], David Attias[2,10], Christine Muti[2,8], Marc Sznajder[1], Mireille Claustres[4,5,13], Claudine Junien[8,10,14], Clarisse Baumann[15], Valérie Cormier-Daire[14,16], Marlène Rio[14,16], Stanislas Lyonnet[14,16], Henri Plauchu[17], Didier Lacombe[18], Bertrand Chevallier[1,2,10], Guillaume Jondeau[2,19,20], and Catherine Boileau [2,8,10,14]

A TGFBR2 gene screening



B TGFBR1 gene screening



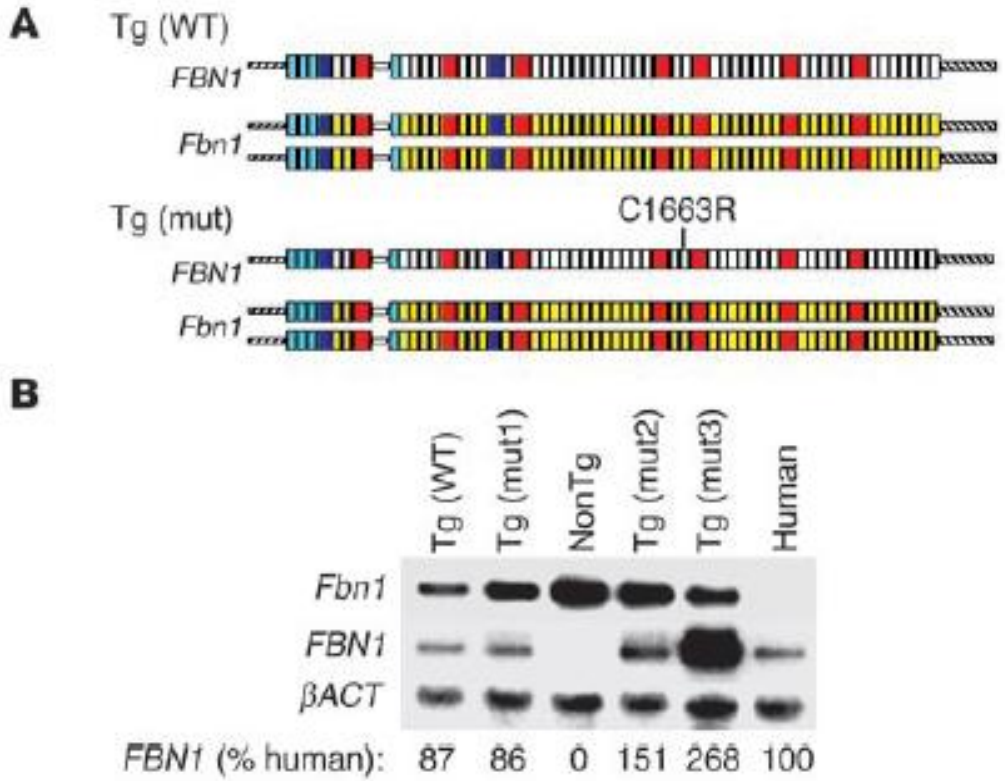
ectopia lentis
Possibile correlazione

Table 3: Comparison between probands carrying a *TGFBR2* gene mutation, probands with no mutation identified in this gene and probands carrying a *FBN1* gene mutation

Major system involvement	Probands with a *TGFBR2* mutation N=23	Probands with no mutation in the *TGFBR2* gene	Comparison between probands with and without mutation in the *TGFBR2* gene	Probands with *FBN1* gene mutation [Faivre et al., 2007]	Comparison between probands with mutation in the *TGFBR2* gene and in the *FBN1* gene
Cardiac	22/23	286/373	p=0.036	776/1013	p=0.041
Ocular	2/21	72/306	NS	542/1013	p=<0.0001
Skeletal	5/21	90/326	NS	327/1013	NS
Neurological	4/8	32/63	NS	154/292	NS
Skin and integument	10/21	139/258	NS	480/1013	NS
Pulmonary	3/22	24/226	NS	73/1002	NS

Patogenesi complessa
Attività dominante negativa della forma mutante
Riduzione severa delle microfibrille e nella matrice depositata da fibroblasti in coltura
Livelli proteici <50%

Psc o delezione
Aploinsufficienza
Insufficiente per l'assemblaggio delle microfibrille



Research article Related Commentary, page 161

Evidence for a critical contribution of haploinsufficiency in the complex pathogenesis of Marfan syndrome

Daniel P. Judge,[1] Nancy J. Biery,[2] Douglas R. Keene,[3] Jessica Geubtner,[1] Loretha Myers,[2] David L. Huso,[4] Lynn Y. Sakai,[3] and Harry C. Dietz[2,5]

[1]Division of Cardiology and [2]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland, USA. [3]Shriners Hospital for Children, Oregon Health and Science University, Portland, Oregon, USA. [4]Department of Comparative Medicine, Johns Hopkins University, Baltimore, Maryland, USA. [5]Howard Hughes Medical Institute, Bethesda, Maryland, USA.

Human Molecular Genetics, 2003, Vol. 12, No. 18 **2269–2276**
DOI: 10.1093/hmg/ddg241

Allelic variation in normal human *FBN1* expression in a family with Marfan syndrome: a potential modifier of phenotype?

Sarah Hutchinson[1], Andre Furger[1], Dorothy Halliday[1], Daniel P. Judge[2], Andrew Jefferson[3], Harry C. Dietz[2], Helen Firth[4] and Penny A. Handford[1,*]

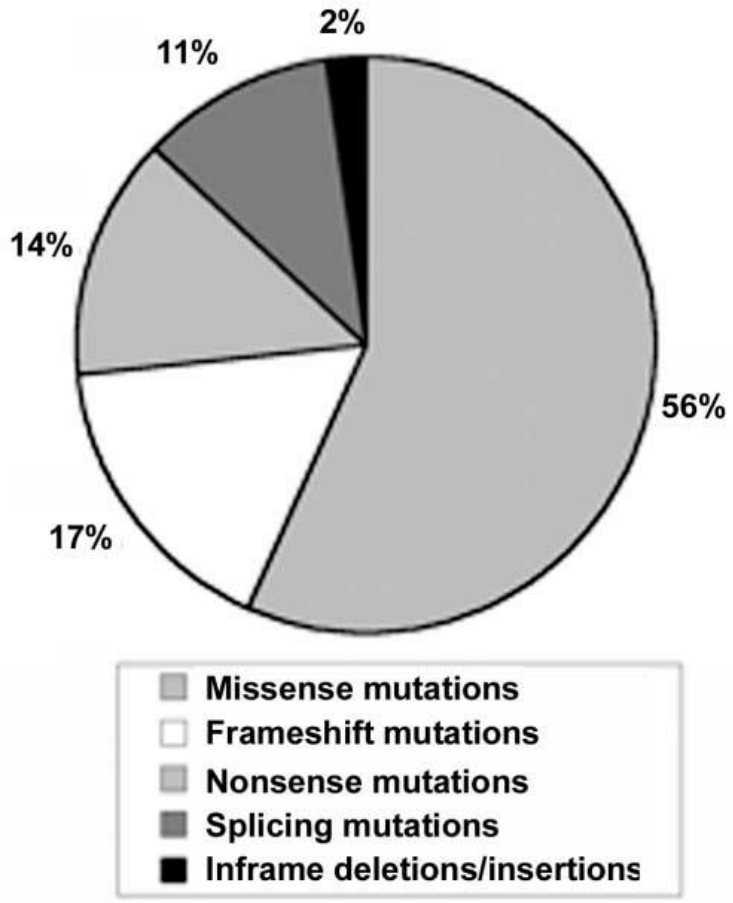
[1]Department of Biochemistry, University of Oxford, Oxford OX1 3QU, UK, [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [3]Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Headington, Oxford OX3 7BN, UK and [4]Department of Medical Genetics, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

Gene

FBN1 (>600 kb) 65 esoni

1000 varianti patogenetiche

Nessuna variante comune



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Vol. 279, No. 31, Issue of July 30, pp. 32924–32931, 2004
Printed in U.S.A.

Consequences of Cysteine Mutations in Calcium-binding Epidermal Growth Factor Modules of Fibrillin-1*

Received for publication, May 11, 2004
Published, JBC Papers in Press, May 25, 2004, DOI 10.1074/jbc.M405239200

Tillman Vollbrandt‡, Kerstin Tiedemann‡, Ehab El-Hallous‡, Guoqing Lin‡, Jürgen Brinckmann‡, Harald John§, Boris Bätge¶, Holger Notbohm‡, and Dieter P. Reinhardt‖

From the ‡Department of Medical Molecular Biology of the University of Lübeck, D-23538 Lübeck, Germany, §IPF PharmaCeuticals GmbH, D-30625 Hannover, Germany, and ¶Klinikum Neustadt, D-23730 Neustadt, Germany

ARTICLE

Effect of Mutation Type and Location on Clinical Outcome in 1,013 Probands with Marfan Syndrome or Related Phenotypes and *FBN1* Mutations: An International Study

L. Faivre, G. Collod-Beroud, B. L. Loeys, A. Child, C. Binquet, E. Gautier, B. Callewaert, E. Arbustini, K. Mayer, M. Arslan-Kirchner, A. Kiotsekoglou, P. Comeglio, N. Marziliano, H. C. Dietz, D. Halliday, C. Beroud, C. Bonithon-Kopp, M. Claustres, C. Muti, H. Plauchu, P. N. Robinson, L. C. Adès, A. Biggin, B. Benetts, M. Brett, K. J. Holman, J. De Backer, P. Coucke, U. Francke, A. De Paepe, G. Jondeau, and C. Boileau

correlazioni genotipo fenotipo

- meccanismi genetici differenti (dominante negativo versus aploinsufficienza)
- funzioni fisiologiche

(strutturale versus mediatore di TGFb)

Correlazione genotipo fenotipo

Solo in alcuni casi

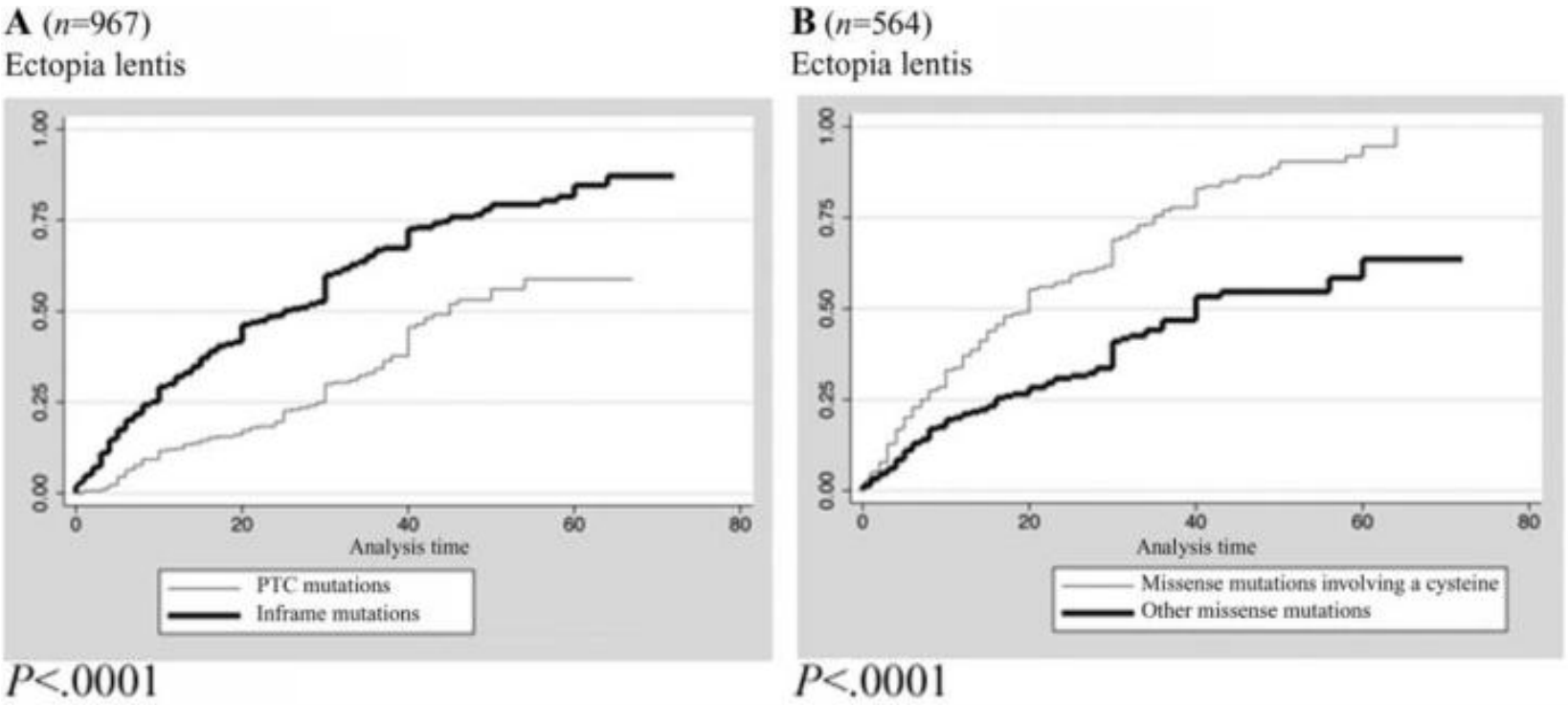
Niente di definitivo

Valore prognostico basso

Generalità

Mutazioni in frame loss/gain (delezioni-inserzioni-errori di splicing) associazione con forma severa

Mutazione missense Cys+/Cys- Ectopia lentis



Dietz HC, Pyeritz RE.

Marfan syndrome and related disorders

. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds.

The Metabolic and Molecular Bases of Inherited Disease.

8 ed. New York, NY: McGraw-Hill. 2001:5287-311.

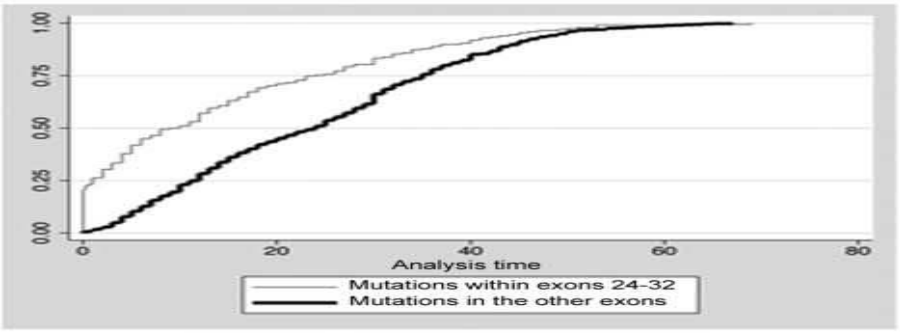
Table 3. Comparison of Probabilities of Clinical-Feature Diagnosis at a Specific Age for Patients with MFS and Other Type I Fibrillinopathies, According to the Type or Location of *FBN1* Mutations

Clinical Feature	*n*	Frequency (%)	Probabilities of Clinical Features Diagnosis (%) at Age 10	25	40	*n*	Frequency (%)	Probabilities of Clinical Features Diagnosis (%) at Age 10	25	40	*P*[a]
	PTC Mutations					Inframe Mutations					
Age at diagnosis of type I fibrillinopathy	319	100.0	20.4	51.7	85.2	665	100.0	32.3	61.2	86.9	.0103
Ascending aortic dilatation	259	81.2	10.6	38.7	76.9	491	73.8	20.2	43.5	73.8	.7791
Aortic dissection in the population presenting with ascending aortic dilatation	65	25.1	.0	3.6	31.1	78	15.9	.2	5.1	22.9	.2014
Aortic surgery in the population presenting with ascending aortic dilatation	102	39.4	.0	9.4	42.0	147	29.9	1.8	12.2	40.4	.5301
Survival	303	95.0	99.7	98.8	95.1	43	6.5	95.5	94.4	93.2	.2311
	Missense Mutations Involving a Cysteine					Other Missense Mutations					
Age at diagnosis of type I fibrillinopathy	348	100.0	32.8	62.6	89.1	225	100.0	28.9	57.8	82.2	.0983
Ascending aortic dilatation	262	75.3	21.3	46.3	75.6	158	70.2	17.6	37.4	69.4	.0797
Aortic dissection in the population presenting with ascending aortic dilatation	41	15.6	.0	4.6	29.9	25	15.8	.7	5.2	10.8	.4249
Aortic surgery in the population presenting with ascending aortic dilatation	80	30.5	1.3	14.0	47.4	49	31.0	2.7	10.4	29.0	.2712
Survival	330	94.8	96.5	96.1	94.5	14	6.2	96.0	93.5	93.5	.6785
	Exons 24–32					Other Exons					
Age at diagnosis of type I fibrillinopathy	198	100.0	51.0	75.8	91.9	815	100.0	23.1	53.7	85.2	<.0001
Ascending aortic dilatation	164	82.8	42.5	65.7	87.3	609	74.7	11.3	36.4	72.4	<.0001
Aortic dissection in the population presenting with ascending aortic dilatation	21	12.8	.7	5.8	28.5	124	20.4	.2	4.3	25.7	.3064
Aortic surgery in the population presenting with ascending aortic dilatation	52	31.7	4.7	17.5	55.2	201	33.0	.5	9.9	38.4	<.0001
Survival	159	80.3	84.5	81.1	76.1	22	2.7	99.6	99.1	97.5	<.0001

NOTE.—All ages are in years. Results are Kaplan-Meier estimates.

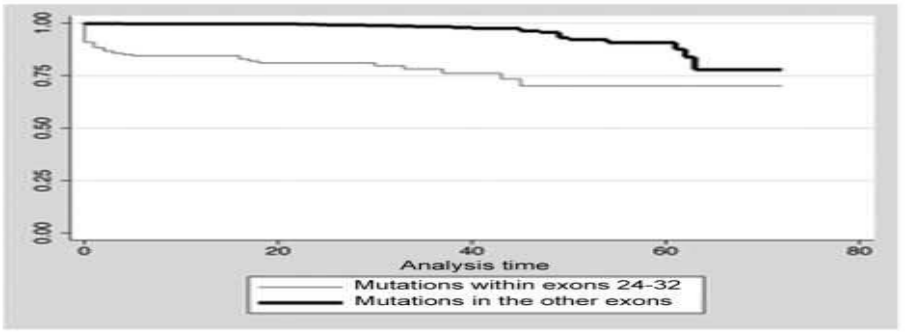
[a] Log-rank test *P* values were for PTC mutations versus inframe mutations, for missense mutations involving a cysteine versus other missense mutations, or for mutations within exons 24–32 versus mutations in other exons.

A (n=1,013)
Age at diagnosis of type I fibrillinopathy



P<.0001

B (n=1,013)
Survival

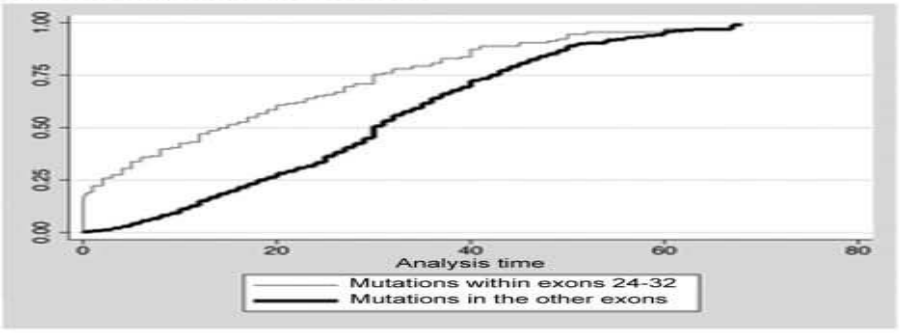


P<.0001

forma severa rapida progressiva (sindrome di marfan neonatale)

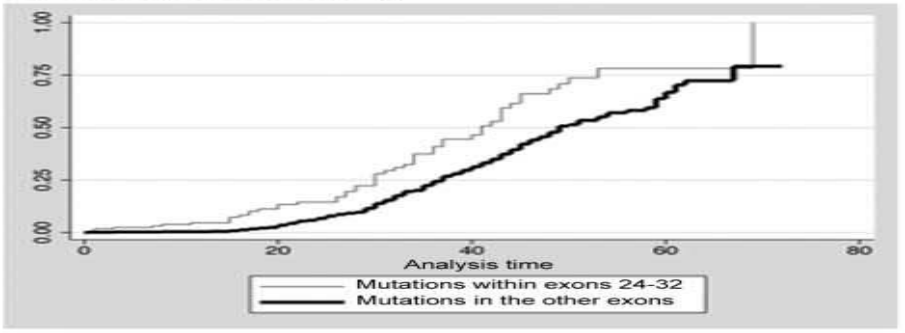
C (n=1,011)
Ascending aortic dilatation

anomalie della valvola mitralica



P<.0001

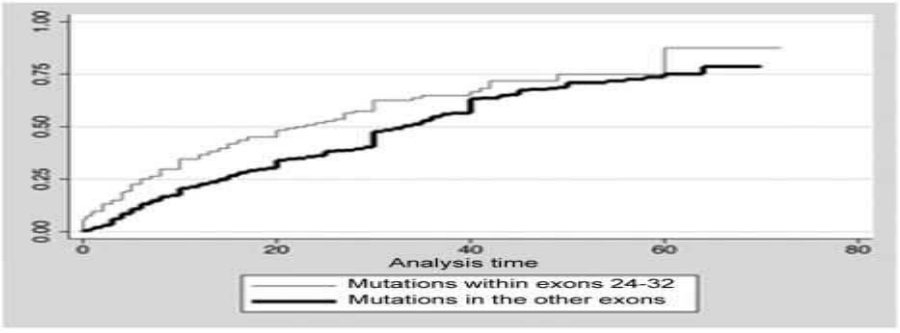
D (n=773)
Ascending aortic surgery



P<.0001

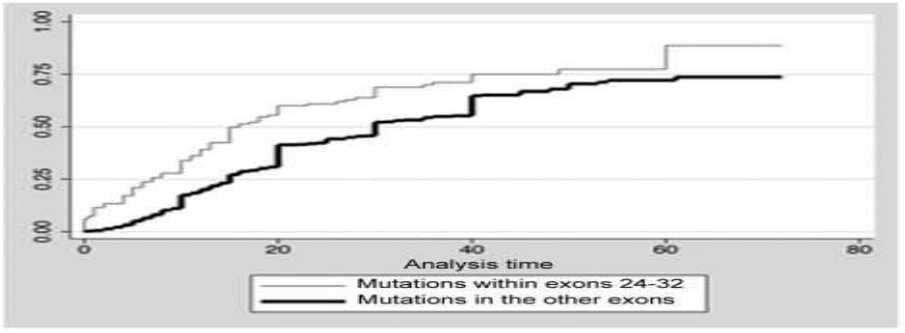
Eccezioni!

E (n=996)
Ectopia lentis



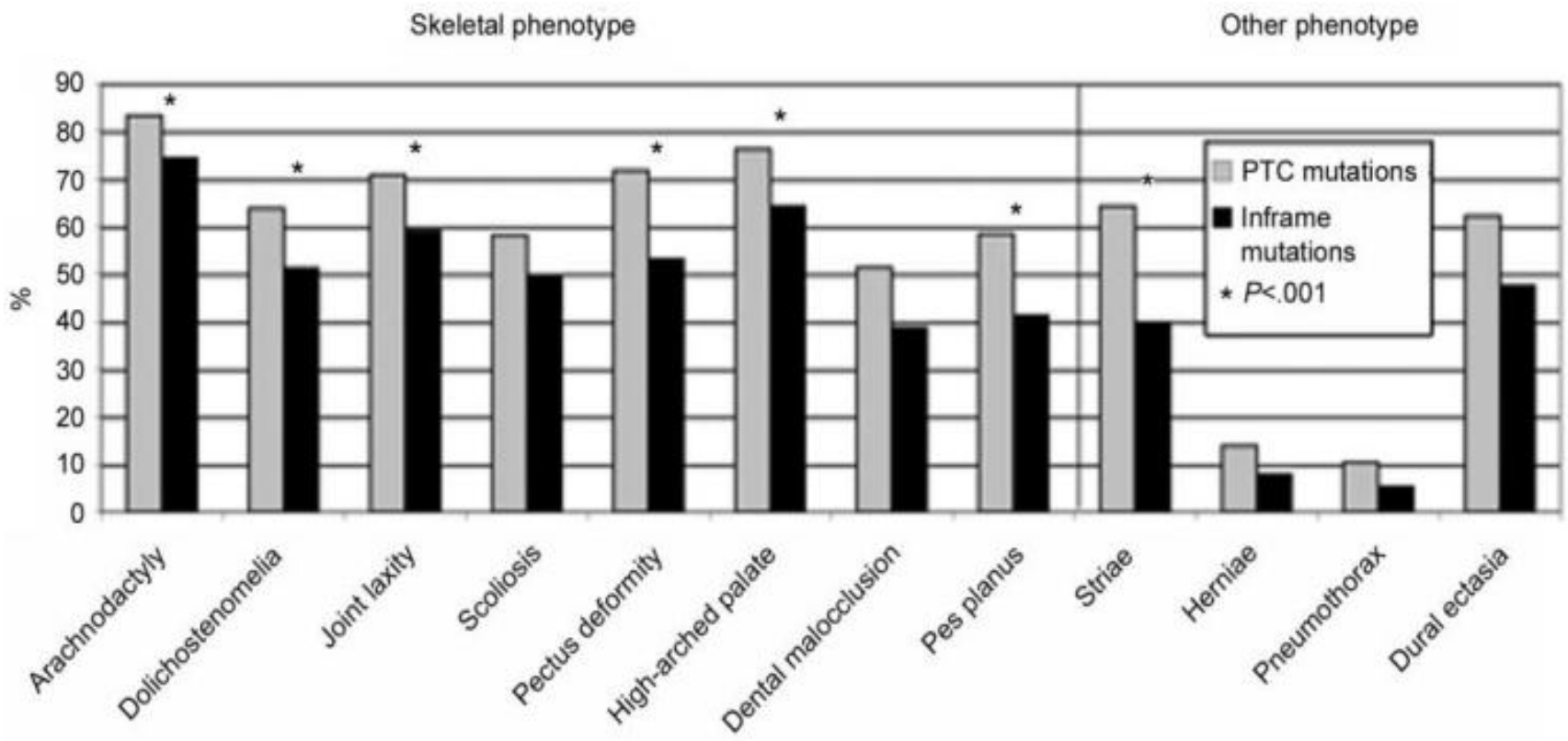
P<.0001

F (n=954)
Scoliosis

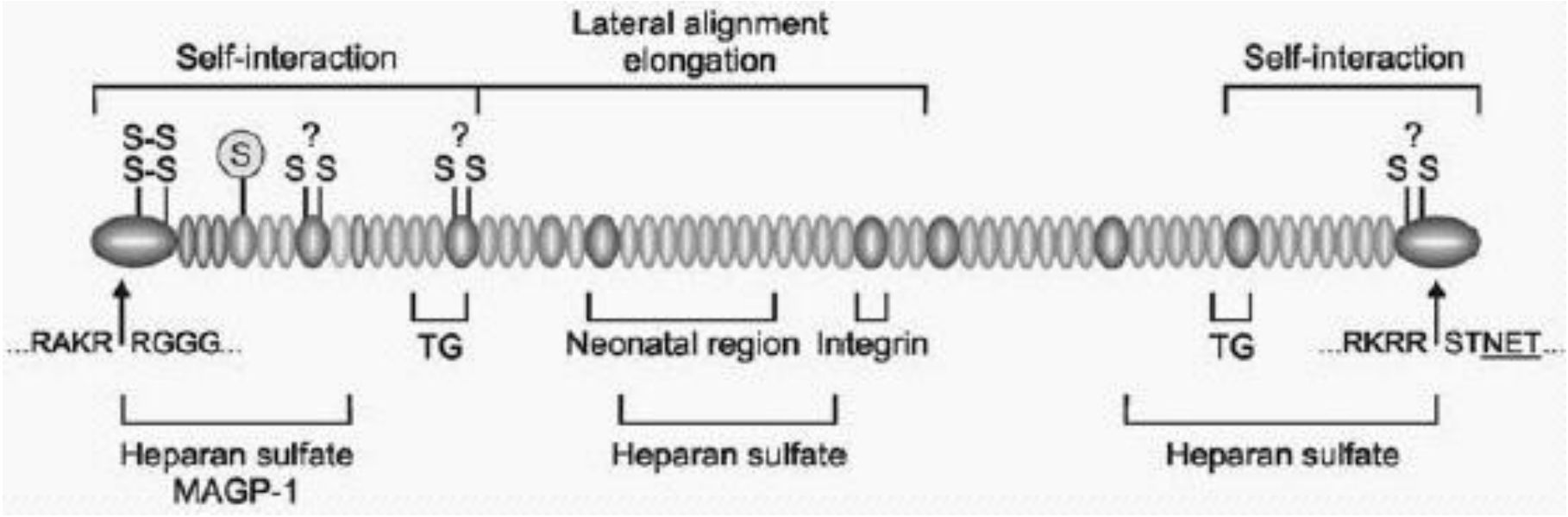


P<.0001

Codone di stop prematuro
degradazione rapida del trascritto
forma mild
Scheletro
derma
Eccezioni !



Varianti patogenetiche che inibiscono il processamento C-terminale
manifestazioni di tipo scheletrico
Sostituzione di aminoacidi strutturalmente funzionali
cisteina -egf calcium binding
forme a severità variabile
Sostituzioni di aminoacidi funzionalmente poco importanti
fenotipo neutro o forme mild (prolasso della valvola mitrale)



Test
strategie
probando
La diagnosi è clinica
presenza di una mutazione già associata alla sindrome è confermativa

Test gene singolo

Test multigenico
pannello Marfan syndrome/Loeys-Dietz syndrome/familial thoracic aortic aneurysms and dissections panel
Variabile per metodi e geni
Sconsigliato in assenza di clinica – rischio di interpretazione erronea

European Journal of Human Genetics (2010) 18; doi:10.1038/ejhg.2010.42

www.nature.com/ejhg

- **Validità analitica**

2 tecniche (dhplc pcr con enzimi di restrizione)
2 set di primer

CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Marfan syndrome type 1 and related phenotypes [*FBN1*]

Mine Arslan-Kirchner*,[1], Eloisa Arbustini[2], Catherine Boileau[3], Anne Child[4], Gwenaelle Collod-Beroud[5], Anne De Paepe[6], Jörg Epplen[7], Guillaume Jondeau[8], Bart Loeys[6] and Laurence Faivre[9]

- **Sensibilità analitica (test+/mutazione+) 100%**
- **Specificità analitica (test-/mutazione-) 100%**

- **Specificità clinica (test- /malattia-)**

Dipende da variabili (età o storia familiare)
Probabile 100% -caso per caso –no data

- **Sensibilità clinica (test+/malattia +)**

Dipende da
variabili (età ,storia familiare)
metodo di screening
criteri clinici richiesti per la diagnosi molecolare
Alta se pazienti soddisfano I criteri di Ghent
Cause
Eterogeneità genetica (TGFBR1 e TGFBR2)
Metodi utilizzati (regioni UTR o introniche)

•valore predittivo clinico positivo (test+/rischio di sviluppare la malattia) ~ 100%.

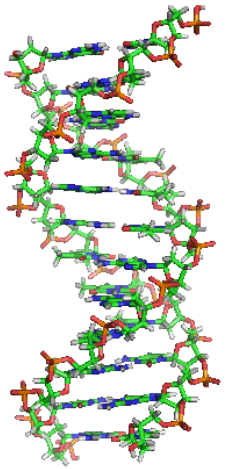
Casi eccezionali penetranza incompleta
Manifestazioni età dipendente
Bambino a rischio
Possibilità di non soddisfare i criteri di ghent nel follow up

•valore predittivo clinico negativo (test-/rischio di sviluppare la malattia)

Considerare
 il rischio aumentato basato sulla storia familiare del soggetto non affetto
Eterogeneità allelica e di locus
Caso indice nella famiglia testato: ~100%

- **Screening mutazioni FBN1**

Utile nel follow up e trattamento preventivo della dilatazione dell'arco aortico nei seguenti casi:
Pazienti che non soddisfano i criteri di ghent con segni clinici
ectopia lentis isolata
Pazienti con segni cardiovascolari suggestivi combinati con segni scheletrici
Casi sporadici in età pediatrica



- **Test predittivo in età pediatrica**:

Prole o familiari in età pediatrica di pazienti
La ricerca di mutazioni FBN1 in tali casi dipende da specifiche circostanze
estesa a familiari la cui diagnosi possa modificare:
lo stile di vita (atleti)
l'inizio del trattamento
la frequenza dei controlli clinici

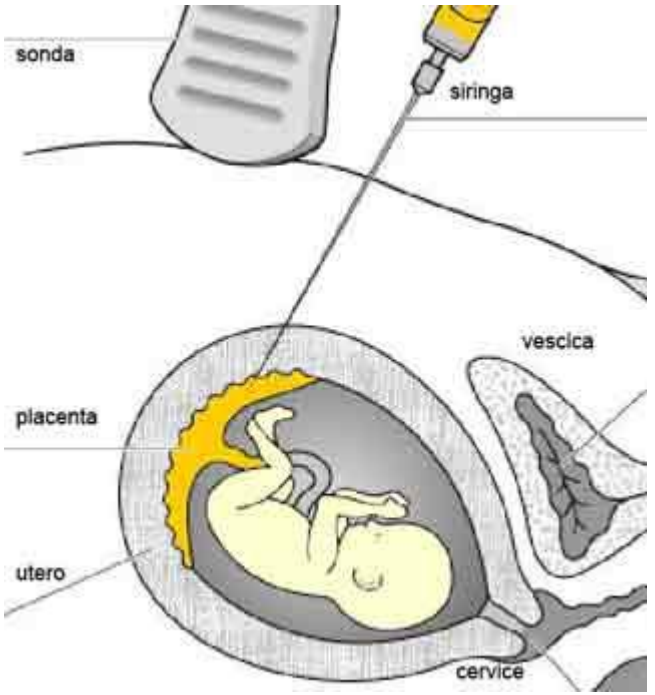
PRENATAL DIAGNOSIS
Prenat Diagn 2002; **22**: 22–28.
DOI: 10.1002/pd.223

Strategies for prenatal and preimplantation genetic diagnosis in Marfan syndrome (MFS)

B. Loeys[1], L. Nuytinck[1], P. Van Acker[1], S. Walraedt[1], M. Bonduelle[2], K. Sermon[2], B. Hamel[3], A. Sanchez[4], L. Messiaen[1] and A. De Paepe[1]*

[1]*Centre for Medical Genetics, Ghent University Hospital, Belgium*
[2]*Centre for Medical Genetics, Dutch-speaking Brussels Free University, Brussels, Belgium*
[3]*Department of Human Genetics, University Medical Centre Nijmegen, The Netherlands*
[4]*Genetic Service, Hospital Clinic, Barcelona, Spain*

- **Diagnosi prenatale**
- Tecnicamente possibile ma quasi mai richiesta
- Analisi DNA estratto dai villi coriali alla 10a 12a settimana di gestazione
- Mutazione familiare
- discussa caso per caso specialmente in famiglie con manifestazioni cardiache severe
- difficoltosa (estrema variabilità fenotipica)



Utilità del test genetico

assenza di storia familiare :

•Dilatazione arco aortico (Z-score ≥2.0) + variante patogenetica FBN1

• segrega in famiglie precedentemente analizzate
•Mutazione de novo (paternità provata e assenza di sintomi nei genitori):
Nonsenso
Delezione/inserzione
Mutazione del sito di splice
Mutazione missenso che crea/distrugge Cys
Mutazione missenso che colpisce un residuo conservato nella sequenza consenso del dominio egf-like

•Ectopia lentis + variante patogenetica FBN1
associata a dilatazione dell'arco aortico

TABLE 1 Revised Ghent Diagnostic Criteria for Marfan Syndrome

Diagnosis of definitive Marfan syndrome (any of the following)
- Aortic root ≥2 *z* score and ectopia lentis
- Aortic root ≥2 *z* score and *FBN1* mutation
- Aortic root ≥2 *z* score and systemic score ≥7
- Ectopia lentis and *FBN1* mutation known to be associated with Marfan syndrome
- Positive family history of Marfan syndrome and ectopia lentis
- Positive family history of Marfan syndrome and systemic score ≥7
- Positive family history of Marfan syndrome and aortic root ≥3 *z* score in those <20 y of age *or* ≥2 *z* score in those >20 y of age

Diagnosis of potential Marfan syndrome
- *FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age

Presenza di mutazioni FBN1 patogenetiche
Z-score <3
Pazienti < 20 AA
Potenziale sindrome di Marfan
Score sistemico <7 e /o dilatazione arco aortico borderline (Z-score <3) in assenza di mutazioni FBN1 patogenetiche
Disordine aspecifico del tessuto connettivo

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Diagnosis of potential Marfan syndrome
- *FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age

TABLE 2 Systemic Scoring System for the Revised Ghent Diagnostic Criteria for Marfan Syndrome (Shown in Table 1)

Feature	Value
Wrist *and* thumb sign	3
Wrist *or* thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity (eg, valgus)	2
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper-to-lower segment ratio *and* increased arm-span-to-height ratio	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Craniofacial features: 3 of the following—dolichocephaly, downward-slanting palpebral fissures, enophthalmos, retrognathia, and malar hypoplasia	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1

Adapted from Loeys et al.[3] Z score calculations are based on Roman et al.[38]

MUTAZIONI E MANAGEMENT DEL PAZIENTE

- **Terapia**

terapia e correzione chirurgica della dilatazione aortica non sono influenzate da presenza/assenza di mutazione
presenza di mutazione influenza follow-up cardiologico e terapia con farmaci per prevenire o limitare la dilatazione aortica

- **Prognosi**

Non è influenzata dalla presenza/assenza di mutazione in FBN1
Mutazioni in TGFBR1/2 correlate con dissecazione aortica a dilatazione minore

- **Consulenza genetica**

il test genetico influenza il counselling:
Test predittivi su bambini o membri della famiglia paucisintomatici
determina il rischio di ricorrenza
Riportati rari casi di mosaicismi germinali o somatici
Utile nel paziente che non soddisfa i criteri di ghent ,in assenza di manifestazioni aortiche
Tutti i pazienti devono essere integrati in una clinica multidisciplinare

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L.A. AA 10

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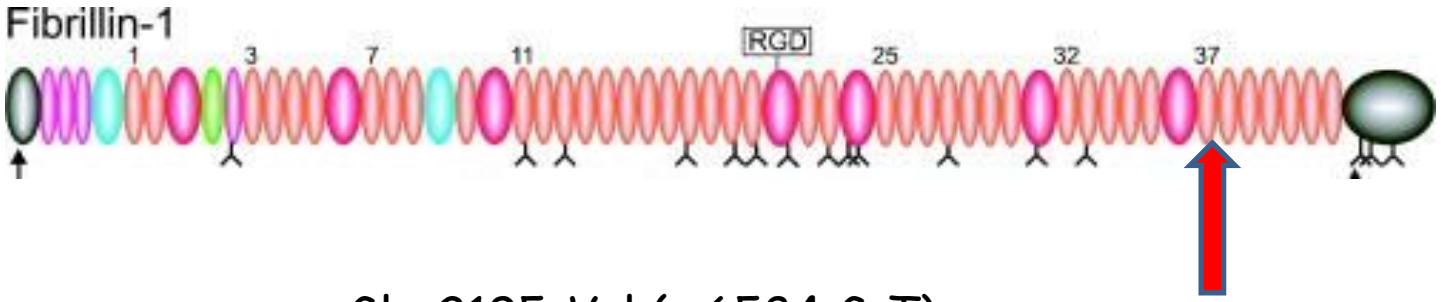
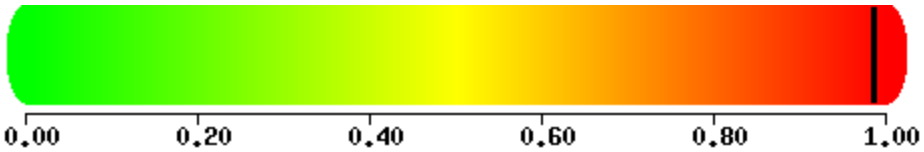


p.Gly-2195-Val (c.6584 G>T)

conserved AA in cbEGF-like [2195-2195]	**4** (0.1 %)

cb EGF-like #37 [2402-2443]	**31** (1 %)



This mutation is predicted to be probably damaging with a score of **0.987** (sensitivity: **0.73**; specificity: **0.96**)

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L.A. AA 10

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Skin striae	1
Myopia	1
Mitral valve prolapse	1

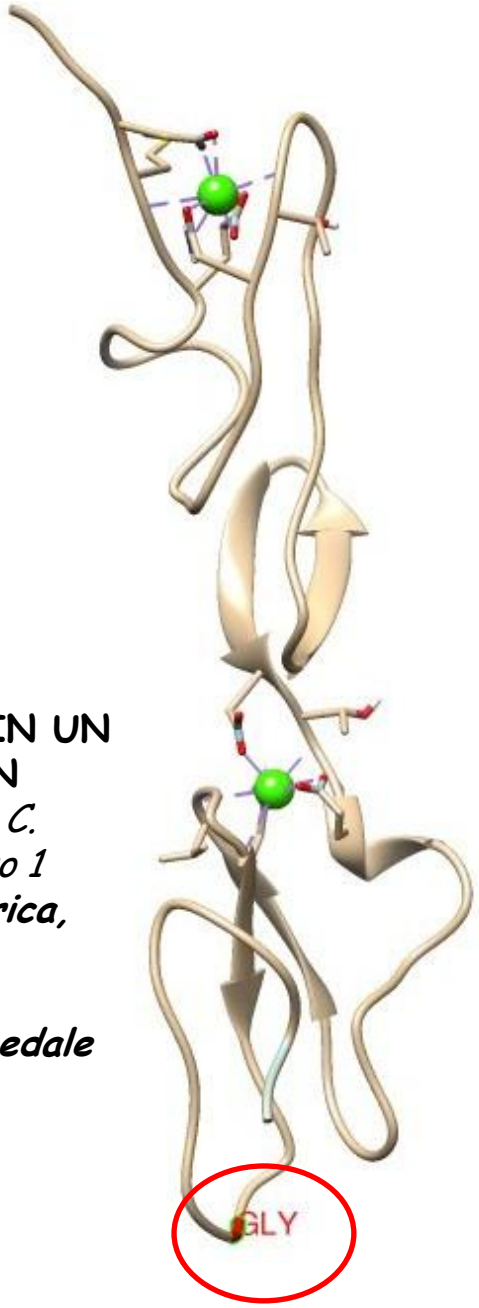
Adapted from Loeys et al.[3] Z score calculations are based on Roman et al.[38]

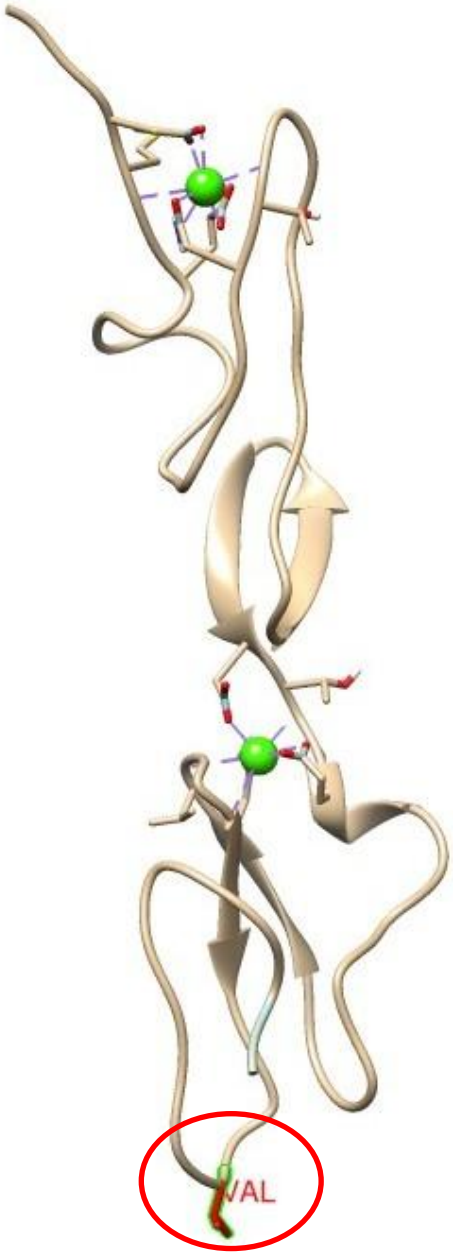
NUOVA MUTAZIONE DEL GENE FBN1 IN UN PAZIENTE CON SINDROME DI MARFAN

V. Procopio 1, P.S. Buonomo 2, M. Amorini 1, C. Liuzzo 1, L. Rigoli 1, A. Bartuli 2, C. Salpietro 1

1 UOC di Genetica e Immunologia Pediatrica, A.O.U. Policlinico "G. Martino", Messina

2 UOC Malattie Rare e Genetica Medica, Dipartimento di Medicina Pediatrica, Ospedale Bambino Gesù, Roma.





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Diagnosis of potential Marfan syndrome

- *FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age

M.F.M. aa 5

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Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
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Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
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Myopia	1
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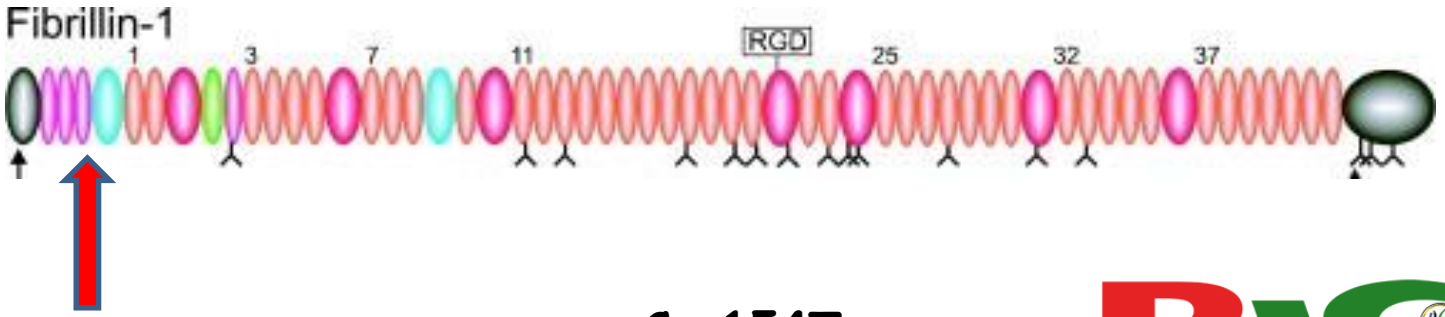
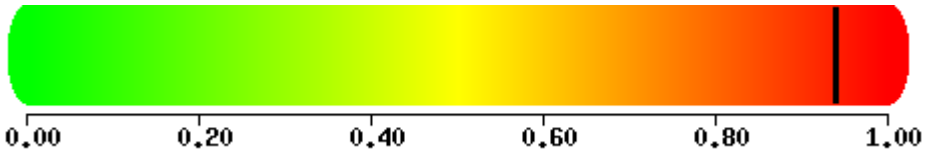
Adapted from Loeys et al.[3] Z score calculations are based on Roman et al.[38]



p. Cys154Tyr

RIGIP
trimestrale di aggiornamento scientifico

Human CLCQKGYIGTHCGQPVCESGCLNGGRCVAPNRCACTYGFTG
Mouse CLCQKGYIGTHCGQPVCESGCLNGGRCVAPNRCACTYGFTG
Pig CLCQKGYIGTHCGQPVCESGCLNGGRCVAPNRCACTYGFTG
Bovine CLCQKGYIGTHCGQPVCESGCLNGGRCVAPNRCACTYGFTG



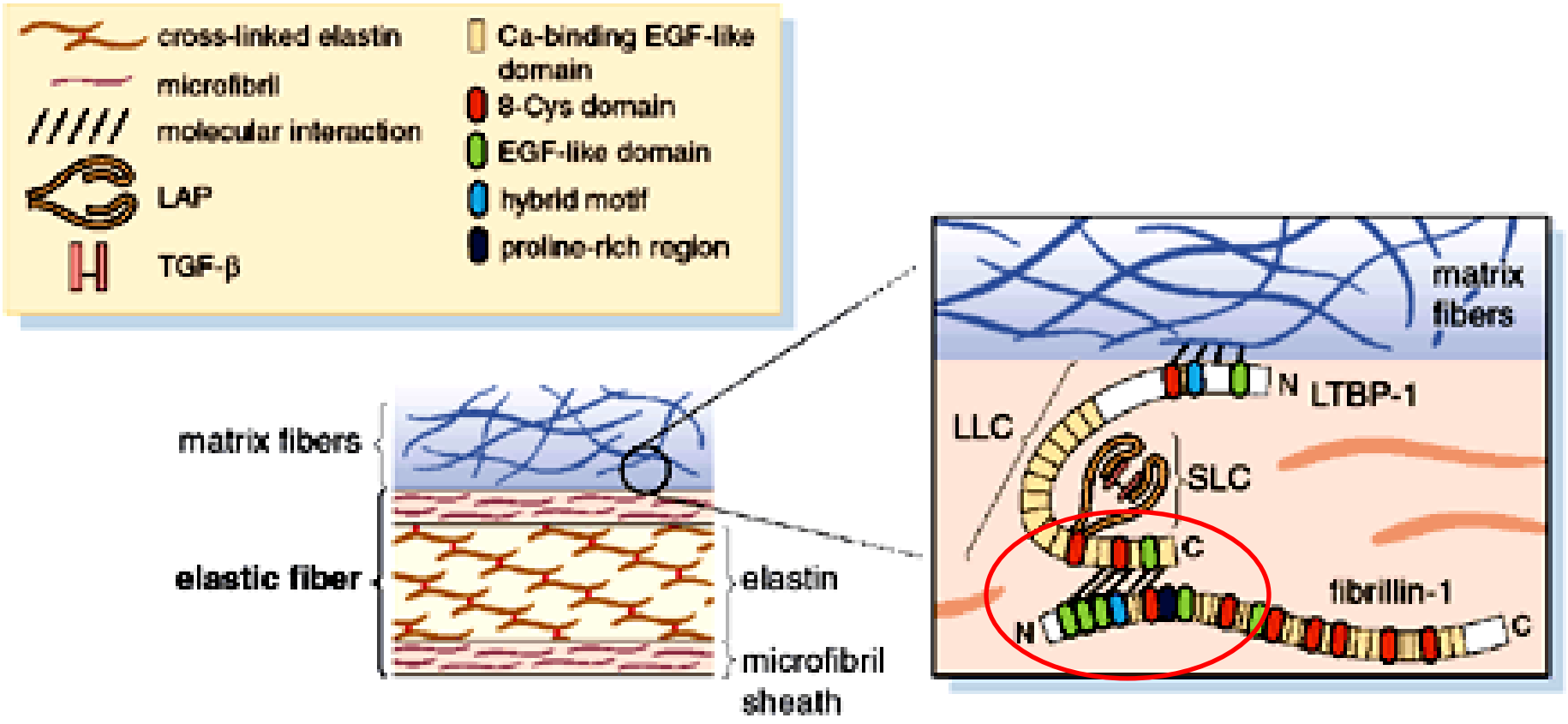
This mutation is predicted to be possibly damaging with a score of **0.940**
(sensitivity: **0.80**; specificity: **0.94**)

Anno IV numero 4 - ottobre 2012

Rivista Italiana di Genetica e Immunologia Pediatrica - Italian Journal of Genetic and Pediatric Immunology

Nuova mutazione del gene FBN1 in un paziente con ectopia bilaterale del cristallino

Procopio V, Liuzzo C, Loddo I, Briuglia S, Rigoli L, Salpietro C
Università di Messina, Dipartimento di Scienze Pediatriche, U.O.C. Genetica ed Immunologia Pediatrica


cross-linked elastin
microfibril
molecular interaction
LAP
TGF-β
Ca-binding EGF-like domain
8-Cys domain
EGF-like domain
hybrid motif
proline-rich region
matrix fibers
elastic fiber
elastin
microfibril sheath
matrix fibers
N
LTBP-1
LLC
SLC
C
fibrillin-1
N
C

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Dural ectasia	2
Protrusio acetabulae	2
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Scoliosis or thoracolumbar kyphosis	1
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Adapted from Loeys et al.[3] Z score calculations are based on Roman et al.[38]

14 aa

p.Cys154Ser

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Diagnosis of potential Marfan syndrome

- *FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age

HUMAN MUTATION Mutation in Brief #678 (2004) Online

MUTATION IN BRIEF

Detection of Thirty Novel *FBN1* Mutations In Patients With Marfan Syndrome or a Related Fibrillinopathy

Andrew Biggin[1], Katherine Holman[1,2], Maggie Brett[1,2], Bruce Bennetts[2,3], and Lesley Adès*[1,3,4]

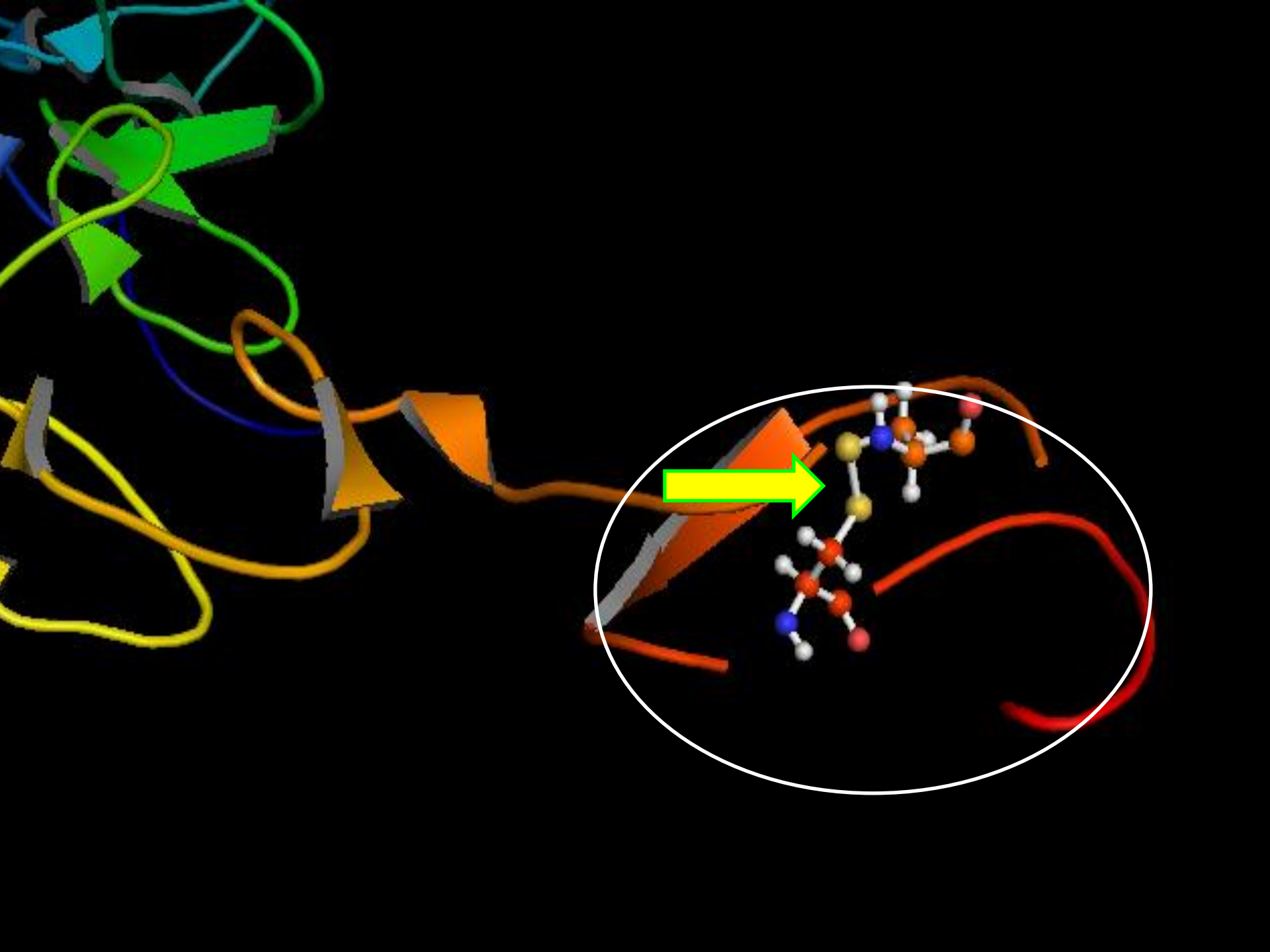
[1]Marfan Research Group, [2]Department of Molecular Genetics, [3]Discipline of Paediatrics and Child Health, [4]Department of Clinical Genetics, The Children's Hospital at Westmead, NSW, Australia

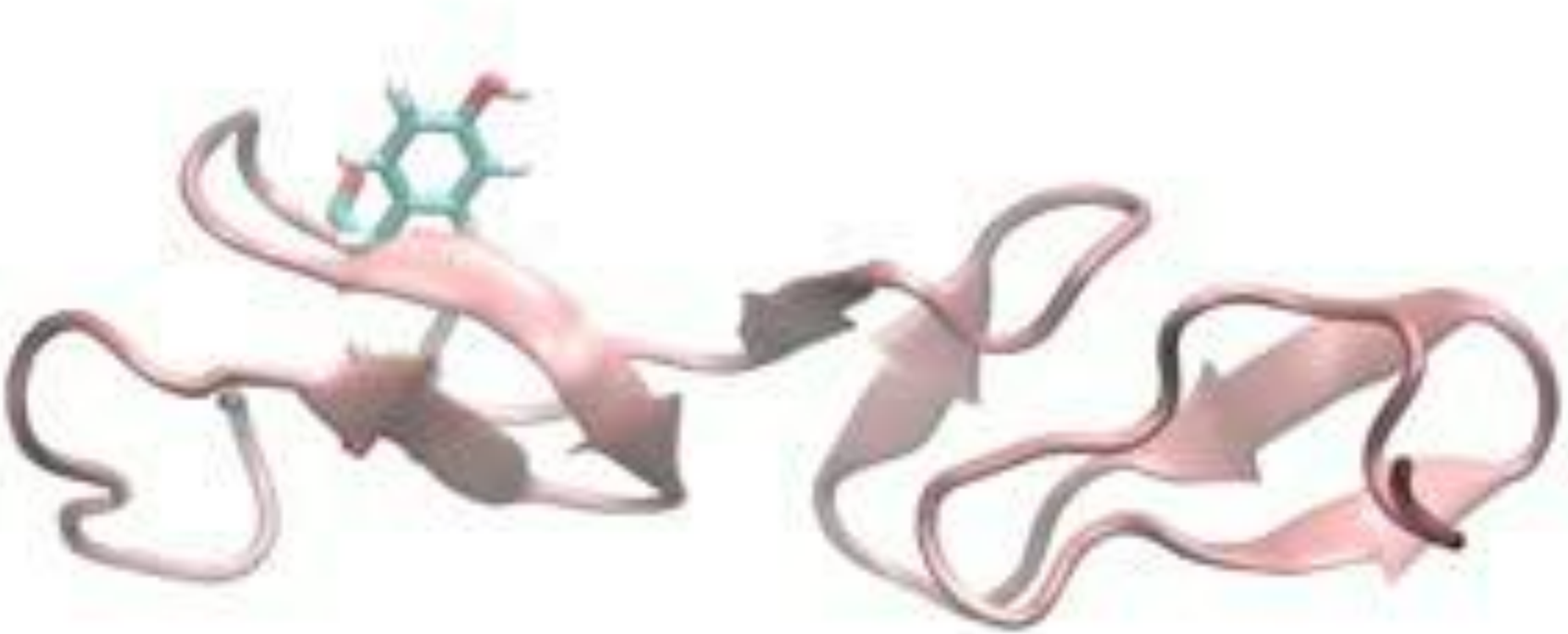
*Correspondence to: Dr. Lesley C Adès, Department of Clinical Genetics, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Australia; Tel.: +61(0)2 9845 3273; Fax: +61(0)2 9845 3204; E-mail lesleya@chw.edu.au

THE MARFAN FOUNDATION

Any of the following findings in an FBN1 screening should be considered causal in making the diagnosis of Marfan syndrome. Marfan syndrome has been positively associated with each of the following:

- Mutation previously shown to segregate in Marfan family
- De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
- Nonsense mutation
- Inframe and out of frame deletion/insertion
- Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
- Missense affecting/creating cysteine residues
- Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
- Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
- Linkage of haplotype for n≥6 meioses to the FBN1 locus





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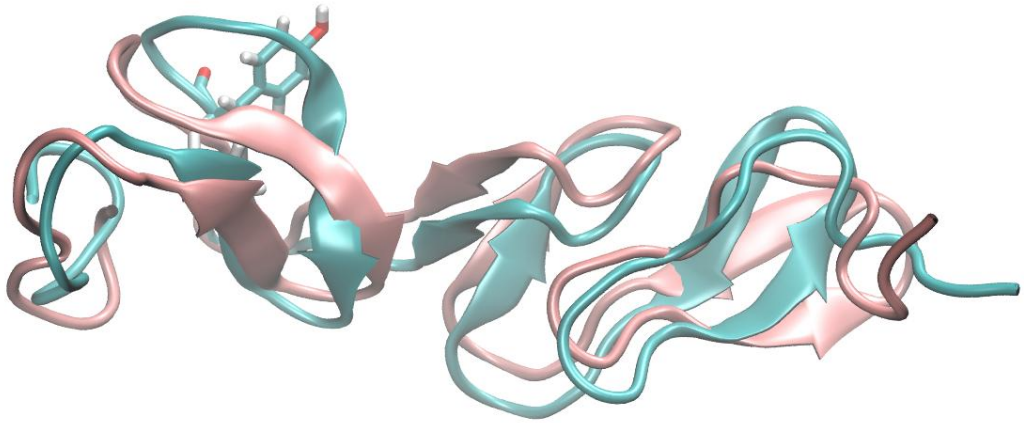

Abstract

Molecular characterization of a de novo mutation in a pediatric patient with isolated ectopia lentis as a diagnostic criterion for Marfan syndrome

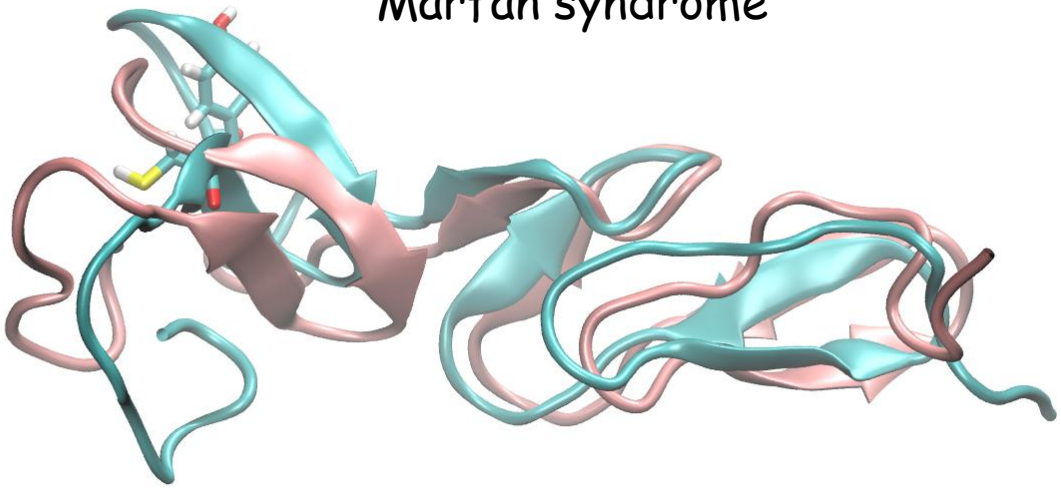

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TABLE 1 Revised Ghent Diagnostic Criteria for Marfan Syndrome

Diagnosis of definitive Marfan syndrome (any of the following)

- Aortic root ≥2 *z* score and ectopia lentis
- Aortic root ≥2 *z* score and *FBN1* mutation
- Aortic root ≥2 *z* score and systemic score ≥7
- Ectopia lentis and *FBN1* mutation known to be associated with Marfan syndrome
- Positive family history of Marfan syndrome and ectopia lentis
- Positive family history of Marfan syndrome and systemic score ≥7
- Positive family history of Marfan syndrome and aortic root ≥3 *z* score in those <20 y of age *or* ≥2 *z* score in those >20 y of age

Diagnosis of potential Marfan syndrome

- *FBN1* mutation with aortic root with a *z* score <3 in those <20 y of age

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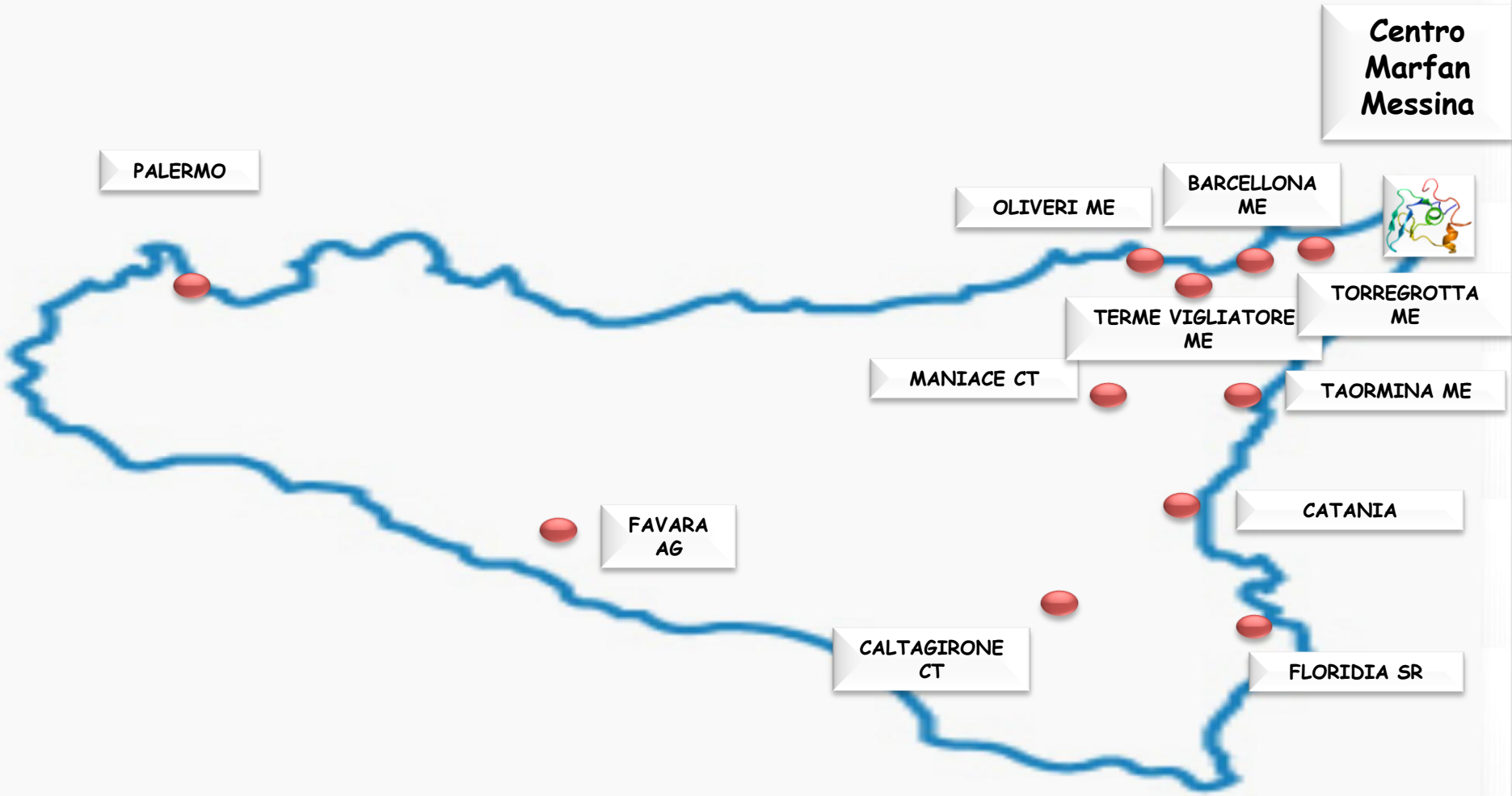
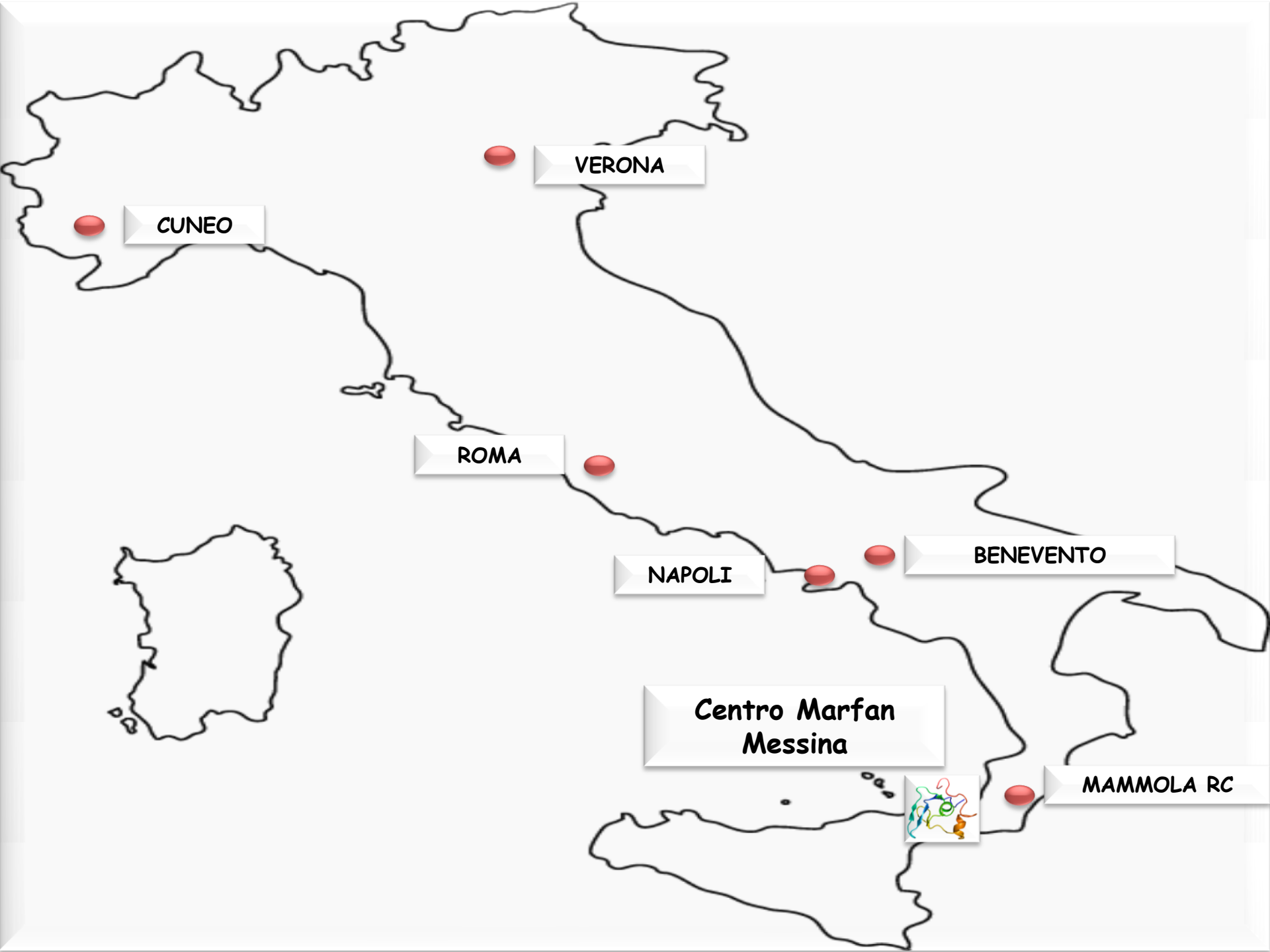
TABLE 2 Systemic Scoring System for the Revised Ghent Diagnostic Criteria for Marfan Syndrome (Shown in Table 1)

Feature	Value
Wrist *and* thumb sign	3
Wrist *or* thumb sign	1
Pectus carinatum	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity (eg, valgus)	2
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper-to-lower segment ratio *and* increased arm-span-to-height ratio	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Craniofacial features: 3 of the following—dolichocephaly, downward-slanting palpebral fissures, enophthalmos, retrognathia, and malar hypoplasia	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1

Adapted from Loeys et al.[3] Z score calculations are based on Roman et al.[38]


Centro Marfan Messina
PALERMO
OLIVERI ME
BARCELLONA ME
TORREGROTTA ME
TERME VIGLIATORE ME
MANIACE CT
TAORMINA ME
CATANIA
FAVARA AG
CALTAGIRONE CT
FLORIDIA SR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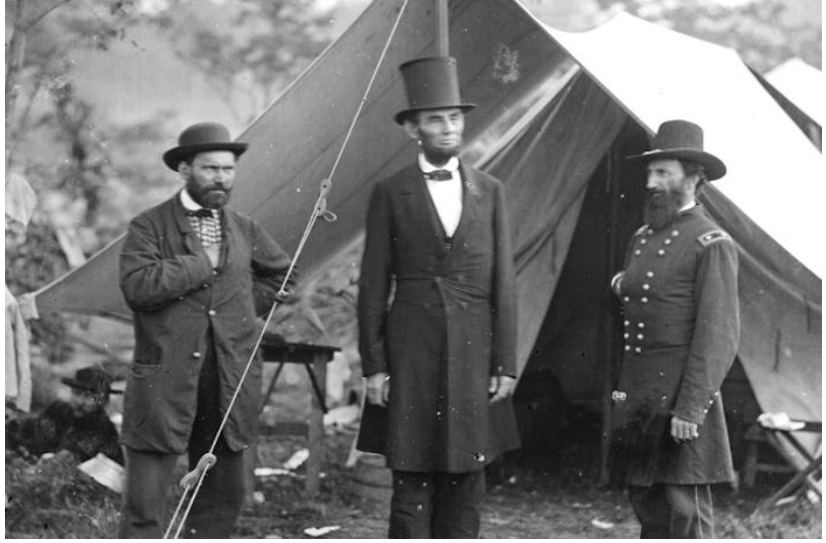
Messina
MAMMOLA RC

Take home

Genetica → clinica

clinica → Genetica ↔ clinica

akenathon



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