MALATTIE RARE E DISABILITA'
"Siamo Rari … ma Tanti"

OTTAVA GIORNATA
DEL DIRITTO COSTITUZIONALE ALLA SALUTE

1999- 2009 IL GRANDE INGANNO

Venerdì 4 dicembre 2009, ore 08.30 – 16.00

Camera dei Deputati
Palazzo Marini – Sala delle Conferenze
Via del Pozzetto, 158
Roma (Piazza San Silvestro)

STUDIARE, DIAGNOSTICARE E PREVENIRE LE MALATTIE RARE: 2000-2009 DIECI ANNI DI IMPEGNO DELL'ISTITUTO CSS-MENDEL.

Prof. Bruno Dallapiccola e Dott.ssa Rita Mingarelli
Istituto CSS-Mendel, Roma

L'istituto Mendel, fondato nel 1953 da Luigi Gedda, ha ospitato nella seconda metà del secolo scorso un centro per lo studio dei gemelli. Donato alla Fondazione Casa Sollievo della Sofferenza alla fine degli anni '90 e riaperto nel 2000 è diventato un centro di riferimento per la Genetica Medica in Italia con un impegno specifico nella ricerca, nelle attività diagnostiche e formative.

Effettua mediamente ogni anno oltre 5.000 diagnosi genetiche, in particolare di citogenetica molecolare, che utilizzano piattaforme altamente tecnologiche, come gli array-CGH e gli SNP-array, e di genetica molecolare, soprattutto rivolta agli studi di patologie mendeliane. L'Istituto offre consulenze di genetica medica di primo e di secondo livello, che si rivolgono in particolare alla patologia prenatale e alle malattie rare.

Nel decennio 2000-2009 l'Istituto ha prodotto circa 350 pubblicazioni. Il valore di *impact factor* del 2009 è superiore a 300 punti.

Relativamente alla ricerca in ambito clinico, sono state identificate o ridefinite a livello nosologico una serie di malattie rare a difetto molecolare non noto, come la sindrome acro-cardio-facciale; la sindrome KGB; la sindrome mastocitosi cutanea-microcefalia-sordità-microtia; la sindrome microcefalia-facio-cardio-scheletrica. E' stato caratterizzato il fenotipo cardiaco di varie patologie, come la sindrome di Goldenhar, di Kabuki, di DiGeorge-Velo-cardio-facciale.

Sono stati mappati numerosi loci di malattie rare, come il gozzo multinodulare legato all'X; l'ipoplasia-aplasia familiare della rotula; la paraplegia spastica tipo SGP19; una forma di neuromiopatia con vacuoli; due forme di sordità genetica ad esordio tardivo (DFNA30, DFNA43); una forma di cheratocono; una forma di scoliosi mendeliana.

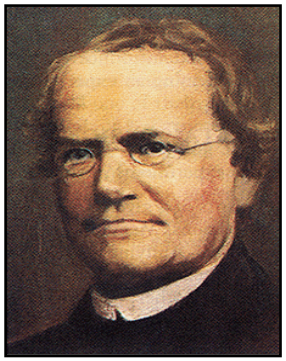
E' stata identificata e mappata una forma rara di candidiasi familiare cronica con deficit di ICAM1 e una forma di telangiectasia familiare benigna. Il gene-malattia è stato successivamente identificato in *RASA1*, che è stato associato ad un quadro clinico più eterogeneo, comprendente la sindrome di Parkes-Weber, l'aneurisma della vena di Galeno e altri difetti vascolari con circolo ematico rallentato. Sono stati mappati e clonati i geni della sindrome osteoporosi-pseudoglioma (*LRP5*, i cui polimorfismi oggi sappiamo essere anche

fattori di rischio per l'osteoporosi comune); un gene per una forma giovanile familiare autosomica recessiva della malattia di Parkinson (*PINK1,* che conferisce suscettibilità anche alla malattia di Parkinson comune); il gene *EVC1* che è stato correlato sia alla osteocondrodisplasia di Ellis Van Creveld che alla disostosi acro-dentale di Weyers; il gene *PCNT* che è stato correlato al nanismo primitivo osteodisplastico microcefalico tipo II; i geni di due sindromi progeroidi, *SYLBP1*, che è stato correlato al geroderma osteodisplastico, e *PYCR1* alla cutis laxa tipo II autosomica recessiva; sono stati clonati alcuni geni della sindrome di Noonan *(KRAS, SOS1, RAF1, BRAF, SHOC2);* sono state definite le basi molecolari della sindrome LEOPARD (geni *PTPN11, RAF1, BRAF*); sono stati mappati e/o clonati alcuni geni della sindrome di Joubert e delle sindromi correlate al segno neuroradiologico del dente molare (JBTS2, *CEP290, INPP5E*) e il gene per la displasia mandibulo-acrale *(LAMNA).*

Sono state identificate e caratterizzate una serie di nuove sindromi genomiche, compresa la sindrome da delezione 1p36, del3q29, dup16p13, dup1613.3, dup17q23.2 (correlata al gene *TBX2*), dupXq12q13 (correlata al gene *OPHN1*). E' stata identificata la causa della sindrome di Nablus *mask-like face* (del8q21.3q22.1), di alcuni casi della sindrome di Young-Simpson (vari sbilanciamenti genomici), di un sottotipo clinico della sindrome di Mayer-Rokitanski-Kuster-Hauser (del17q12).

L'istituto è stato impegnato nello sviluppo di alcune linee-guida nazionali (ad es. sindrome di Williams; sindrome di Noonan) e europee (sindrome di Williams), ospita la sede del partner italiano della rete europea DYSCERNE, dedicata alla diagnosi dismorfologica, e la sede italiana di Orphanet, il più importante database mondiale per le malattie rare.

Bruno Dallapiccola & Rita Mingarelli
Istituto CSS-Mendel, Roma



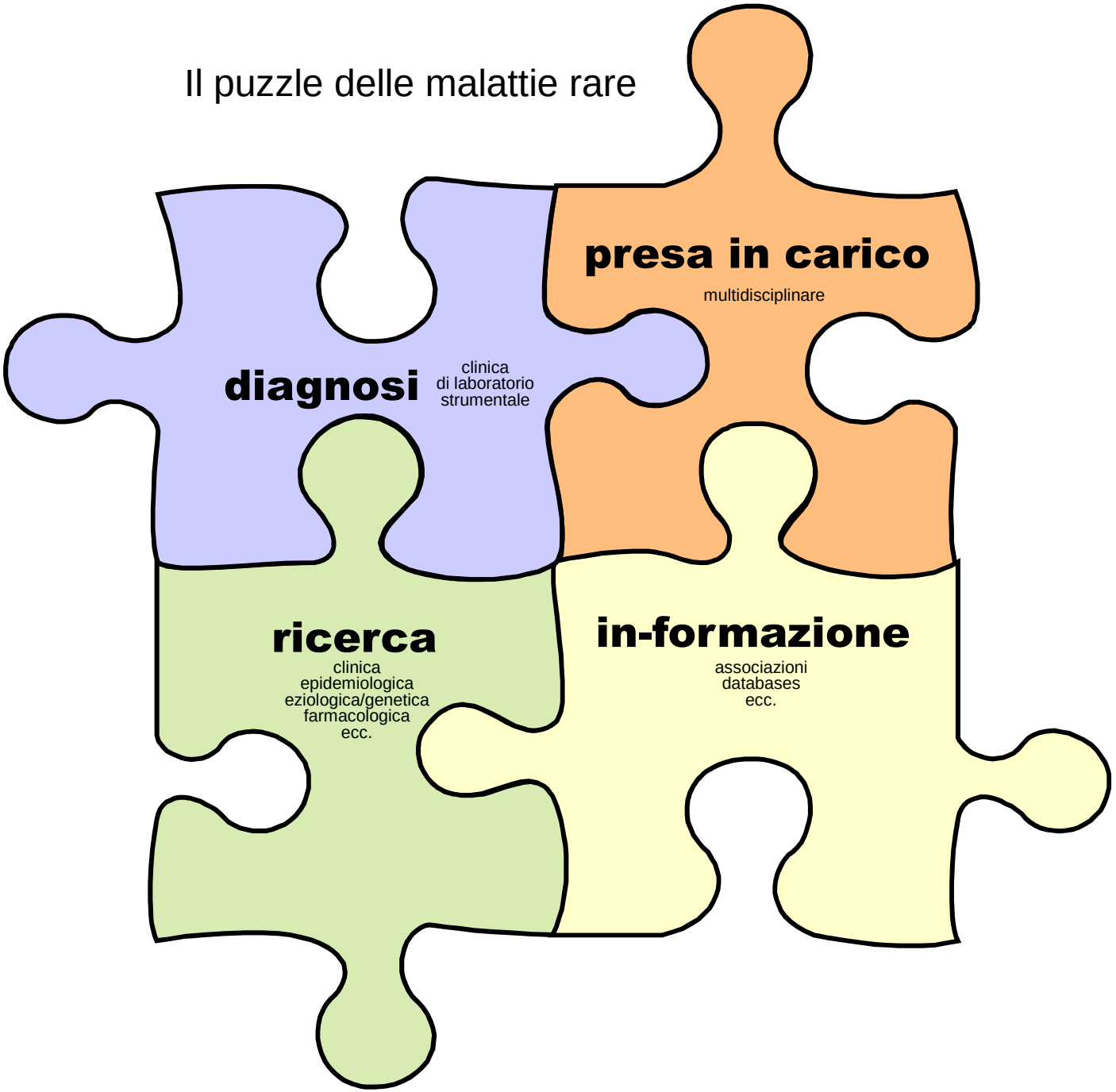




Studiare, diagnosticare e prevenire le malattie rare: 2000-2009 dieci anni di impegno dell'Istituto CSS-Mendel

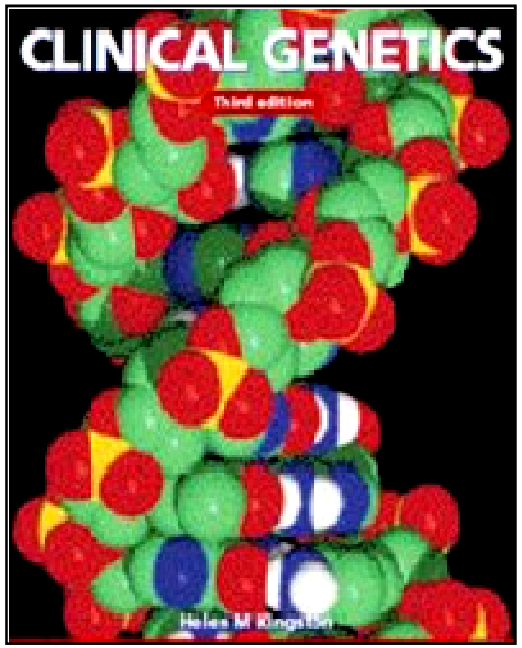
Malattie Rare e Disabilità
Associazione Culturale Giuseppe Dossetti
Roma 4 dicembre 2009

Il puzzle delle malattie rare

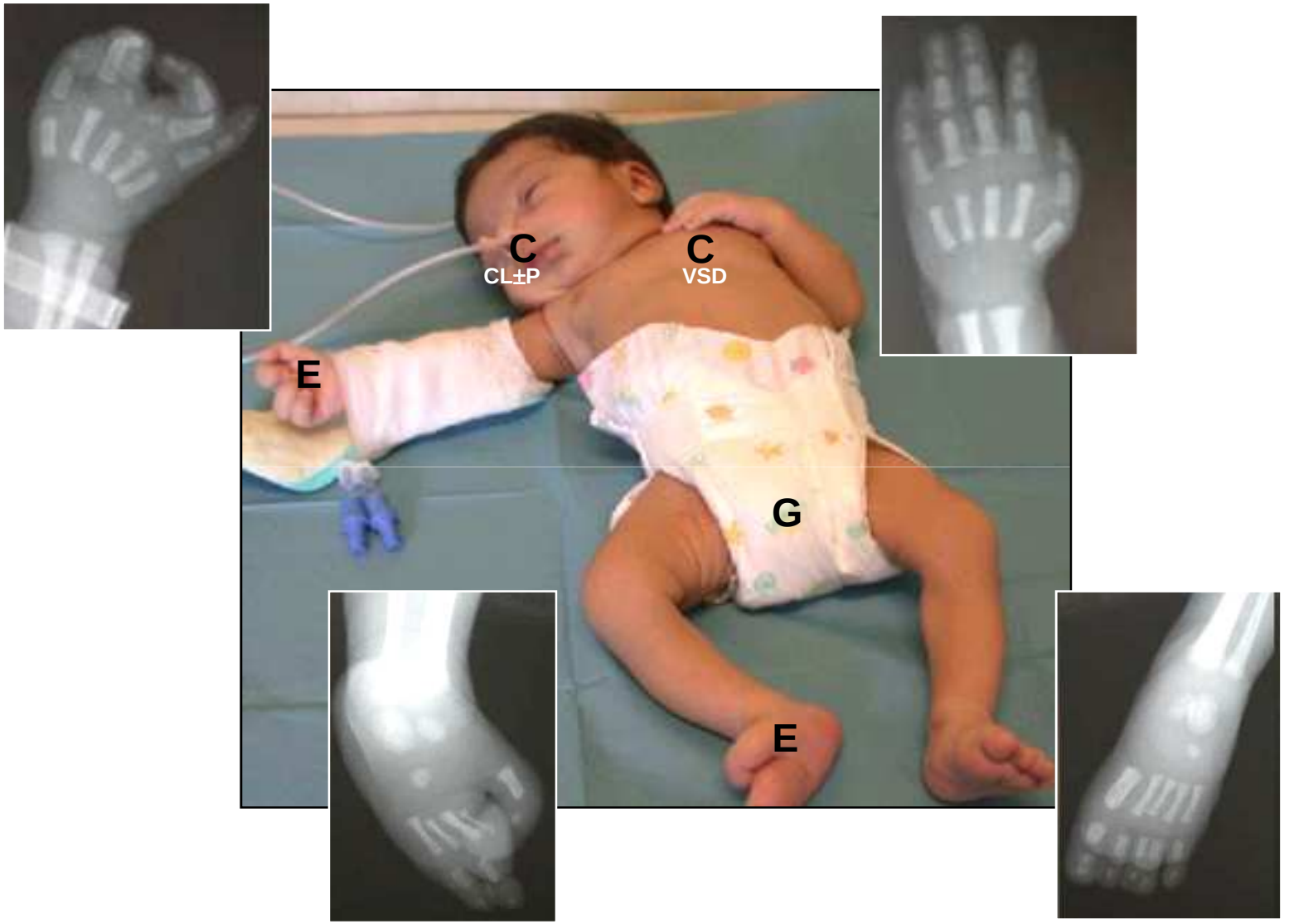




Genetica Clinica



Sindrome acro-cardio-facciale (CCGE, ACFS - OMIM 600460)



Mingarelli R, Zuccarello D, Digilio MC, Dallapiccola B: A new observation of acro-cardio-facial syndrome substantiates interindividual clinical variability. Am J Med Genet A, 136:84-6, 2005

Sindrome di Oliver (OMIM 258200)

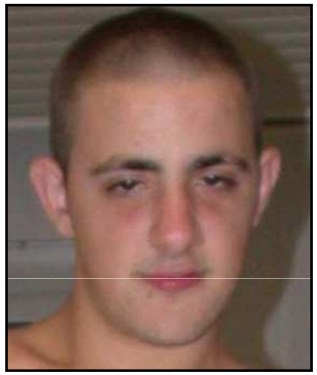
American Journal of Medical Genetics 139A:159–161 (2005)

Research Letter

Report of a Third Family With Oliver Syndrome

Carmelo Damiano Salpietro,[1] Silvana Briuglia,[1] Graziella Bertuccio,[1] Luciana Rigoli,[1] Rita Mingarelli,[2] and Bruno Dallapiccola[2]*

[1]*Department of Pediatric Sciences, University of Messina, Messina, Italy*
[2]*Department of Experimental Medicine and Pathology, CSS-Mendel Institute, La Sapienza University, Rome, Italy*








	Present report		Oliver [1940]	Stevenson and Wilkes [1983]	
Features	Patient 1	Patient 2	Cases 1–3	Case 1	Case 2
Body asymmetry	+	+	?	–	–
Prominent jaw	+	+	?	+	+
Postaxial polydactyly of fingers	+	+	+	+	+
Camptodactyly of fingers	–	+	?	+	?
Clinodactyly of 5th fingers	+	+	?	?	?
Cutaneous syndactyly of fingers	+	+	?	+	?
Fingertip pads	+	+	?	?	?
Postaxial polydactyly toes	–	+	+	–	–
Brachy-syndactyly of toes	–	+	?	+	+
Seizures	+	+	?	+	+
Mental retardation	+	+	+	+	+
Indistinct/absent speech	–	+	+	+	+
Others	Malocclusion, high-arched palate, scoliosis	Microcephaly, malocclusion, high-arched palate, scoliosis	Supernumerary nipples	Prominent eyebrows, short philtrum, absent ear lobes, elbows/knees contractures	Hypoplastic ear lobes, hyperconvex nails

Salpietro CD, Briuglia S, Bertuccio G, Rigoli L, Mingarelli R, Dallapiccola B: Report of a third family with Oliver syndrome. Am J Med Genet 139A(2):159-61, 2005.

Sindrome microcefalia-facio-cardio-scheletrica (OMIM 612946)

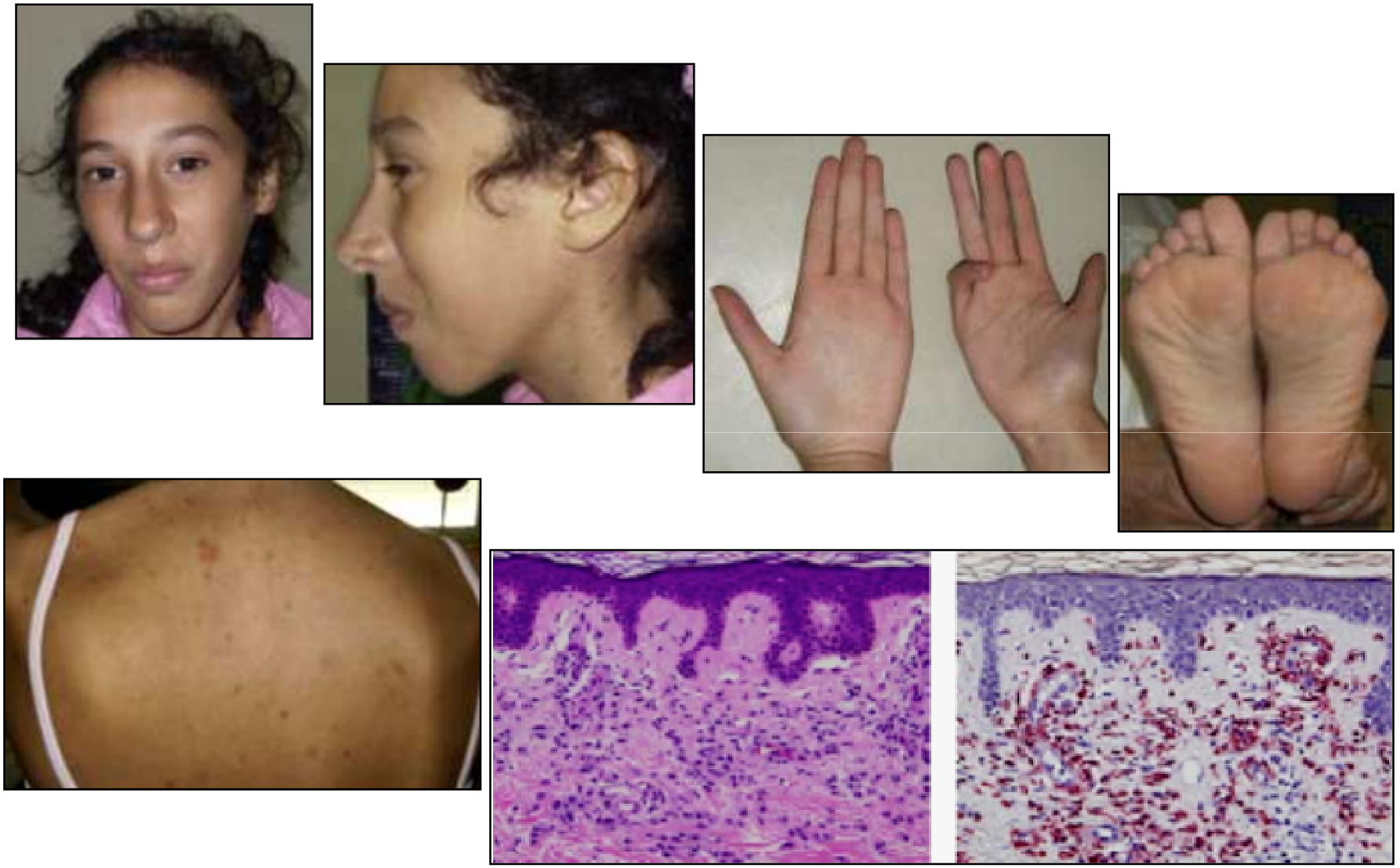




Dallapiccola B, Digilio MC, Zatterale A, Galeone R, Mingarelli R: Confirmation of microcephaly-facio-cardio-skeletal Hadziselimovic type syndrome, Clin Dysmorphol, 18:135-8, 2009

Clinical features	Hadziselimovic		Present report		
	Case 1	Case 2	Case 1	Case 2	Case 3
Low birth weight	+	+	+	+	+
Short stature	+	+	+	+	+
Microcephaly	+	+	+	+	+
Low anterior hairline	+	+	+	+	+
Hypotelorism	+	+	+	+	+
Epicanthic folds	+	+	-	-	+
Ptosis of eyelids	-	+	-	-	+
Strabismus	+	+	-	-	+
Prominent nasal bridge	+	+	-	-	+
Thick/prominent lips	+	+	+	+	+
High-arched palate	+	-	+	+	+
Low set/dysmorphic ears	+	+	+	+	+
Hypoplastic thumbs	+	+	+	+	+
Hypoplastic 1st metacarpals	+	+	+	+	+
Short/dislocated radius	-	+	-	-	+
Delayed bone age	+	+	-	-	-
Congenital heart defect	PA, ASD VSD, OA	-	ToF	-	ToF
High-pitched voice	+	+	-	-	-
Mental retardation	+	+	+	+	+
Hypotonia	-	-	+	+	-
Other	hypoplastic right tibia, long fingers/toes	renal hypoplasia, urinary reflux, imperforate anus, long fingers/toes	2nd-3rd toes Syndactyly	2nd-3rd toes syndactyly, anaemia, hypoplastic corpus callosum and cerebellum	hypoplastic ulna and pubic bones carpal anomalies long toes

Mastocitosi cutanea, microcefalia, sordità, microtia (OMIM 248910)



Salpietro CD, Briuglia S, Cutrupi MC, Gallizzi R, Rigoli L, Dallapiccola B: Apparent third patient with cutaneous mastocytosis, microcephaly, conductive hearing loss, and microtia. Am J Med Genet, 149A:2270-3, 2009.

Network europeo per la diagnosi dismorfologica

I nodi
I partner

Jill Clayton-Smith, Bronwyn Kerr, Dian Donnai & Kay Metcalfe
Manchester, UK (Lead Partner)

Koenraad Devriendt
Leuven, BELGIUM

Nicole Philip
Marseille, FRANCE

Bruno Dallapiccola
Rome, ITALY

Han Brunner & Ineke Van der Burgt
Nijmegen, NETHERLANDS

Malgorzata Krajewska-Walasek & Krystyna Chrzanowska
Warsaw, POLAND

Amsterdam	Iasi	Poznan Prague
Ankara	Istanbul	Rennes
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Barcelona	Leiden	Roma
Belfast	Lille	Rotterdam
Benevento	Lisbon	Sk
Bergen	Ljubljana	So
Bordeaux	London	St olm
Bratislava	Lyon	Tartu
Brussels	Maastricht	Tel Aviv
Cardiff	Madrid	Tirana
Coimbra	Milano	Utrecht
Copenhagen	Montpellier	Valletta
Dijon	Naples	Vienna
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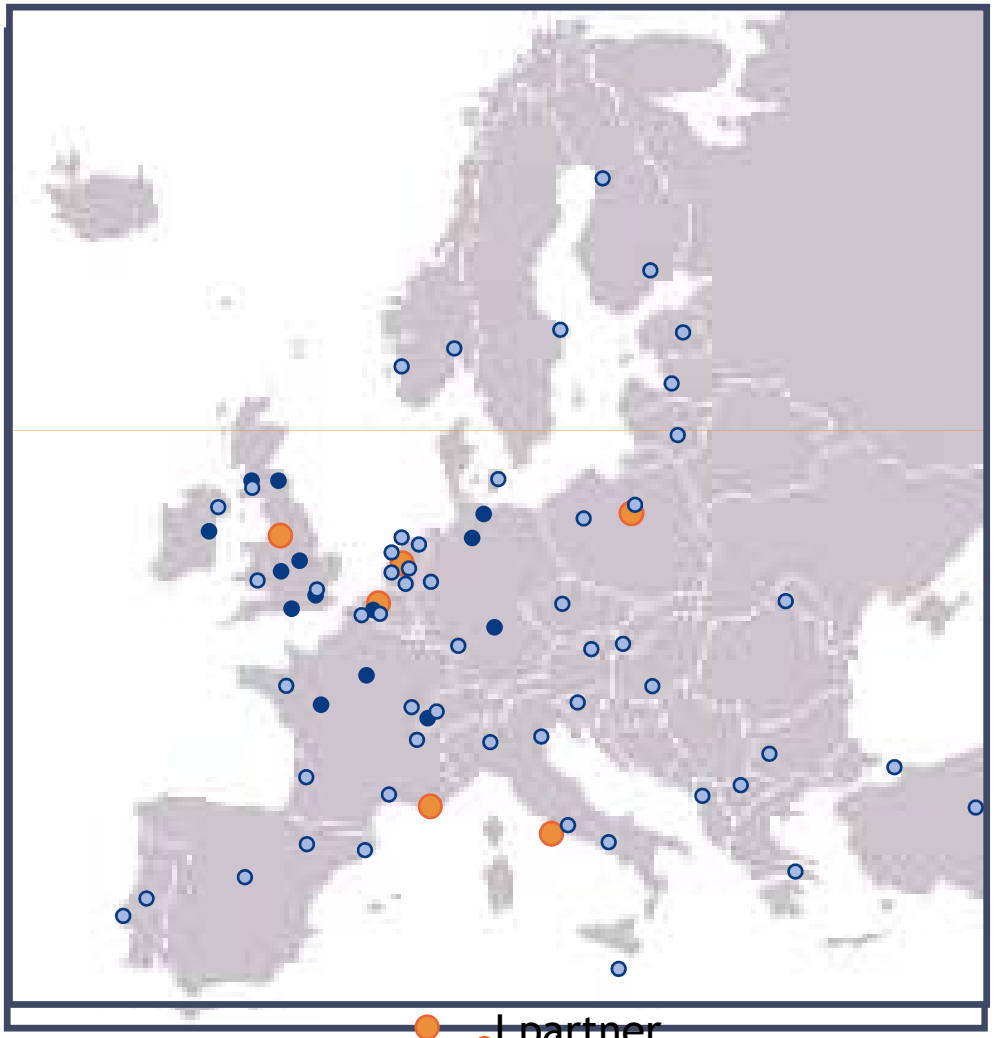
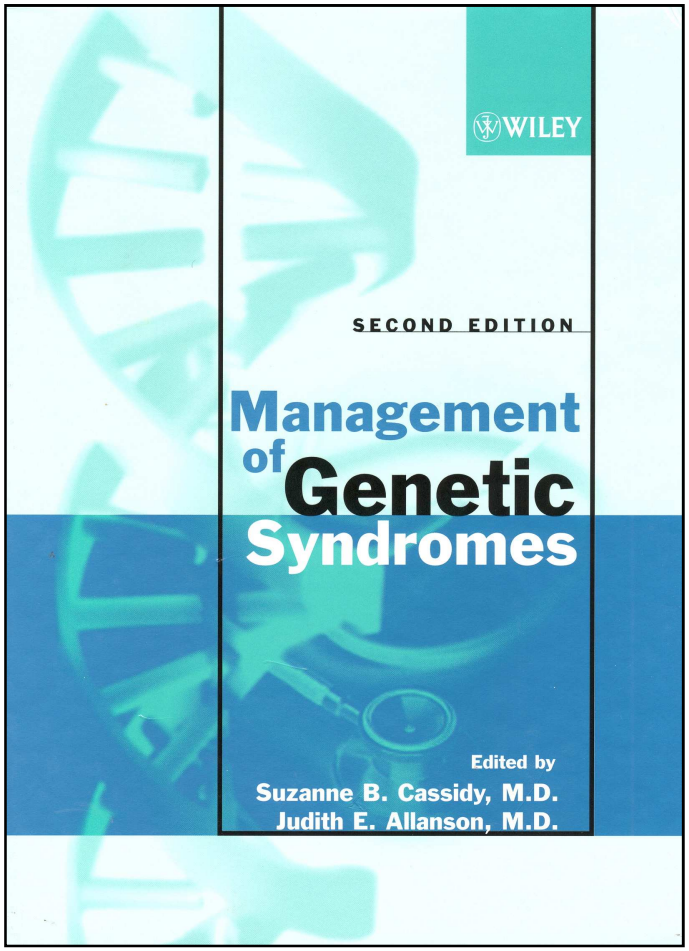
Groningen	Oulu	Zaragoza
Heidelberg	Padova	
Helsinki	Pécs	



- I partner
- Il gruppo degli esperti
- I nodi

- **I partner di DYSCERNE e i componenti del gruppo degli esperti possono registrare i casi al DDS.**
- **78 nodi sono abilitati alla registrazione**

Linee-guida



ITAL J PEDIATR 2006;32:145-155

UPDATE ARTICLE
ARTICOLO DI AGGIORNAMENTO

Noonan's syndrome and related disorders: clinical-molecular update and guidelines

Sindrome di Noonan e sindromi correlate: caratteristiche clinico-molecolari e linee guida

A. SARKOZY[1,2], M.C. DIGILIO[3], B. MARINO[4], R. MINGARELLI[1,2], M. TARTAGLIA[5,6], B. DALLAPICCOLA[1,2]
[1] IRCCS-CSS, "San Giovanni Rotondo" and CSS-"Mendel" Institute, Rome, Italy; [2] Department of Experimental Medicine and Pathology, University "La Sapienza", Rome, Italy; [3] Medical Genetics, "Bambino Gesù" Hospital, IRCCS, Rome, Italy; [4] Section of Pediatric Cardiology, Department of Pediatrics, University "La Sapienza", Rome, Italy; [5] Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Rome, Italy; [6] Department of Pediatrics, "Mount Sinai" School of Medicine, New York, NY, USA



RIV ITAL PEDIATR (LIP) 2000; 26: 244-253

Linee guida per la sindrome di Williams

B. DALLAPICCOLA*,**, R. MINGARELLI**, A. GIANNOTTI***, M.C. DIGILIO***, V. VOLTERRA****, S. VICARI***

PER L'ASSOCIAZIONE ITALIANA SINDROME DI WILLIAMS (AISW) E LA SOCIETÀ ITALIANA DI GENETICA UMANA (SIGU)

* Dipartimento di Medicina Sperimentale e Patologia, Università di Roma «La Sapienza»
** Istituto CSS-Mendel, Roma
*** Ospedale Pediatrico «Bambino Gesù», Roma
**** Istituto di Neuropsicologia del CNR, Roma



Williams Syndrome Clinical Management Guidelines

Management of Williams Syndrome

A Clinical Guideline

Williams Syndrome Guideline Development Group

Dr Jane Ashworth, Dr Susmito Biswas, Professor Bruno Dallapiccola, Dr Mark Dalzell, Dr Jane Deal, Professor Dian Donnai, Pam Griffiths, Dr Kay Hood, Professor Pat Howlin, Dr Ed Ladusans, Dr Ralph MacKinnon, Dr Josephine Marriage, Dr Neil Martin, Dr Kay Metcalfe, Dr Zulf Mughal, Dr Ramanlal Patel, Dr Alison Pike, Dr Christopher Stinton, Kate Strong, Dr Rajat Verma, Dr Mike Wolfman

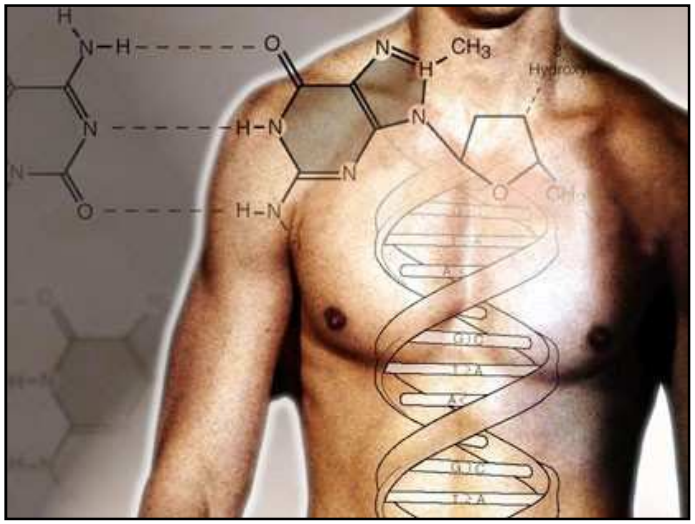
Funded by The Williams Syndrome Foundation UK

with support from DYSCERNE: A Network of Centres of Expertise in Dysmorphology and Nowgen, a Centre for Genetics in Healthcare

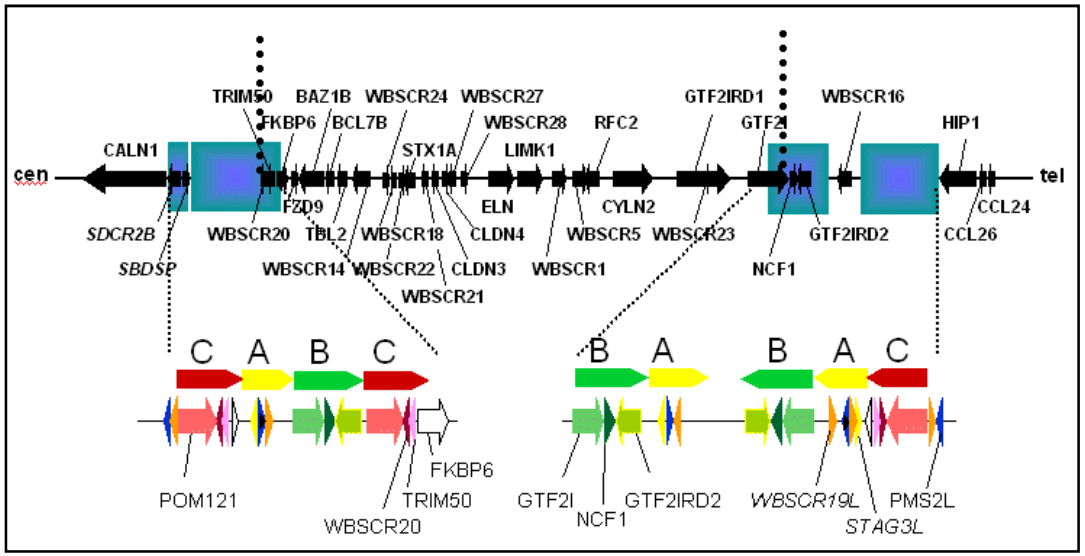
dyscerne

williams SYNDROME FOUNDATION www.williams-syndrome.org.uk

nowgen A Centre for Genetics in Healthcare



Mappatura di geni-malattia



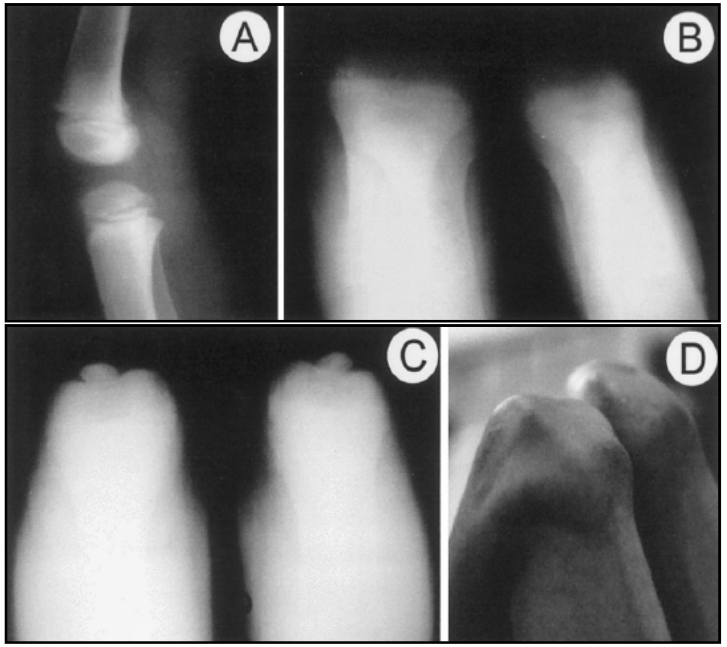
OMIM168860

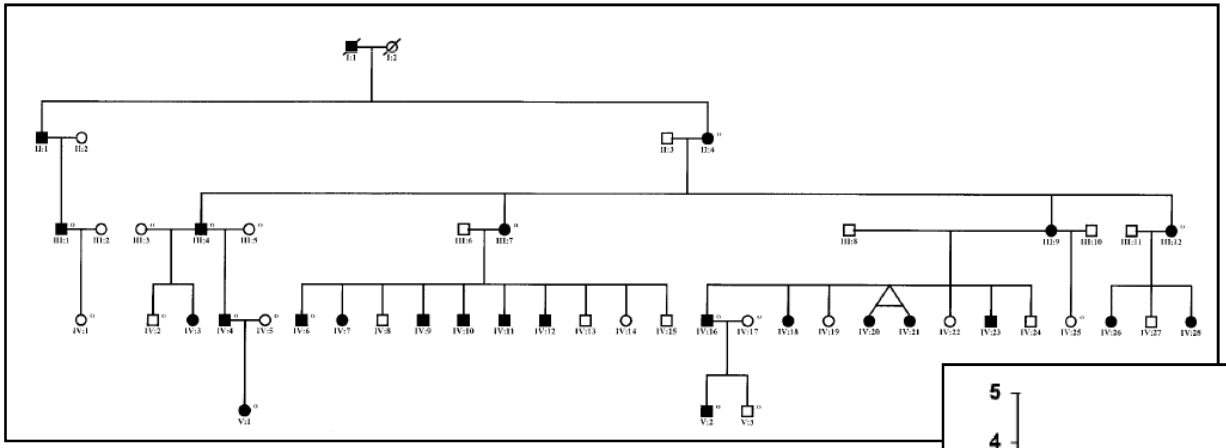
Am. J. Hum. Genet. 65:441–447, 1999

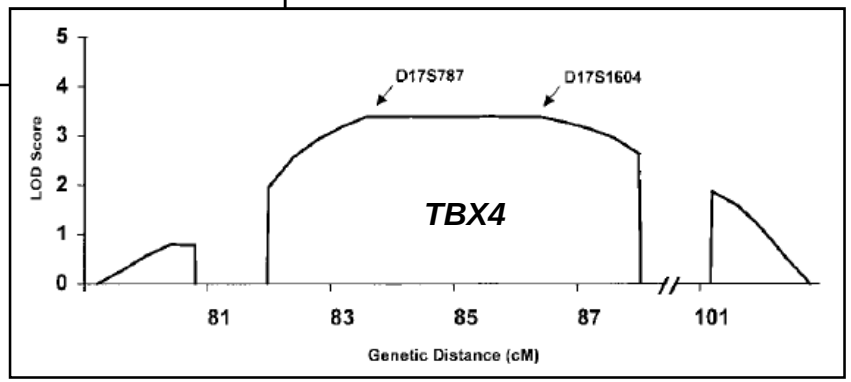
Localization of a Gene for Familial Patella Aplasia-Hypoplasia (PTLAH) to Chromosome 17q21–22

Massimo Mangino,[1] Otto Sanchez,[2] Isabella Torrente,[1] Alessandro De Luca,[1] Francesca Capon,[1] Giuseppe Novelli,[1] and Bruno Dallapiccola[1]

[1]Dipartimento di Biopatologia e Diagnostica per Immagini, Università di Roma Tor Vergata and Istituto CSS-Mendel, Rome; and [2]Unidad de Genetica, Escuela de Medicina, Universidad de Oriente, Ciudad Bolivar, Venezuela







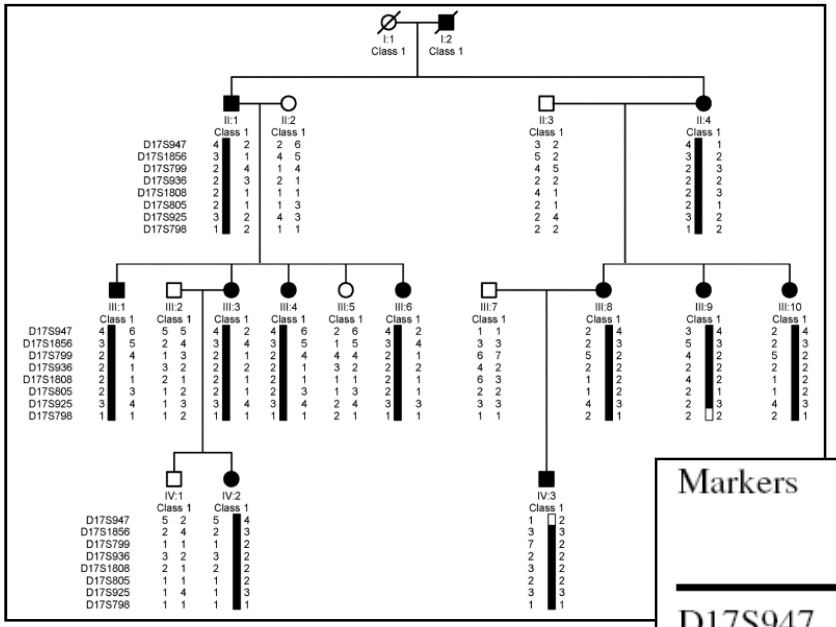
Hum Genet (2002) 111:401–404
DOI 10.1007/s00439-002-0785-4

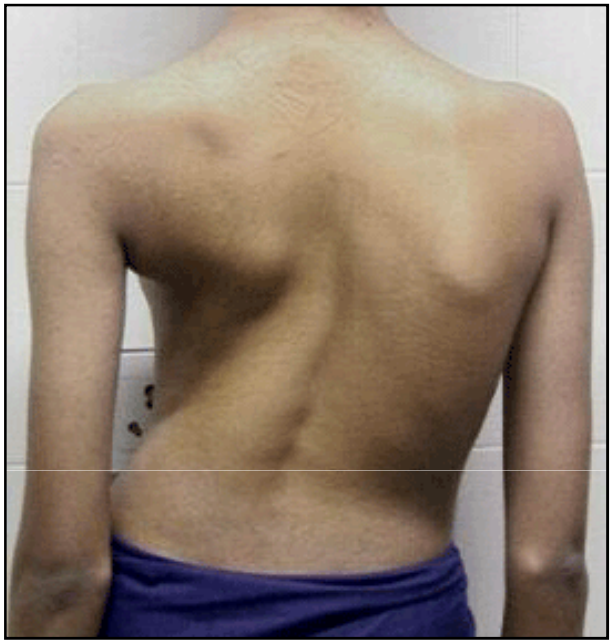
ORIGINAL INVESTIGATION

Leila Baghernajad Salehi · Massimo Mangino
Salvatore De Serio · Domenico De Cicco
Francesca Capon · Sabrina Semprini · Antonio Pizzuti
Giuseppe Novelli · Bruno Dallapiccola

Assignment of a locus for autosomal dominant idiopathic scoliosis (IS) to human chromosome 17p11

(IS2 - OMIM 607354)

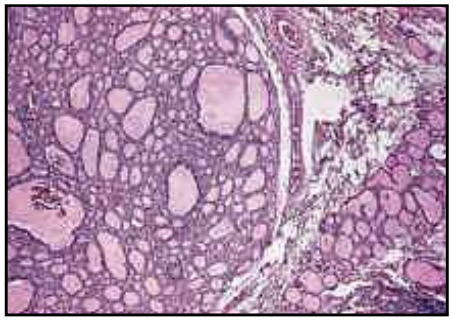




Markers	LOD score at θ=						
	0.00	0.01	0.03	0.05	0.10	0.20	0.30
D17S947	–∞	1.13	1.50	1.62	1.65	1.38	0.93
D17S1856	3.16	3.11	2.99	2.88	2.59	1.97	1.30
D17S799	3.20	3.14	3.03	2.92	2.62	1.99	1.30
D17S936	1.40	1.37	1.32	1.26	1.11	0.80	0.47
D17S1808	2.93	2.87	2.77	2.66	2.39	1.81	1.18
D17S805	3.18	3.13	3.02	2.90	2.61	1.98	1.30
D17S925	3.19	3.14	3.08	2.92	2.63	2.01	1.33
D17S798	–∞	0.62	1.01	1.14	1.22	1.04	0.70

Gozzo multinodulare (MING2 – OMIM 300273)



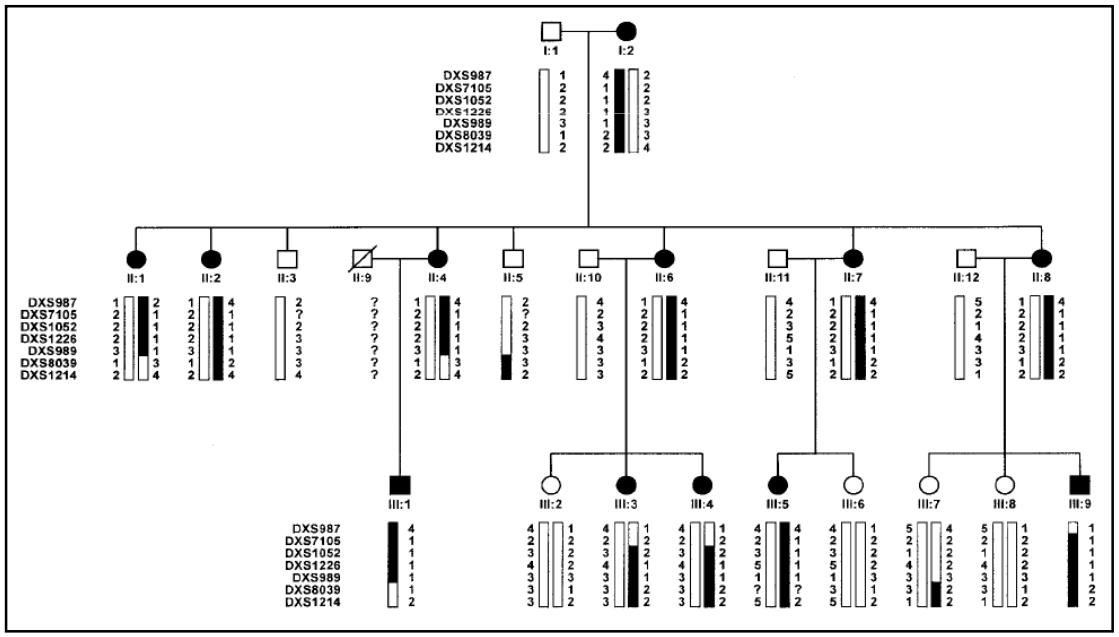


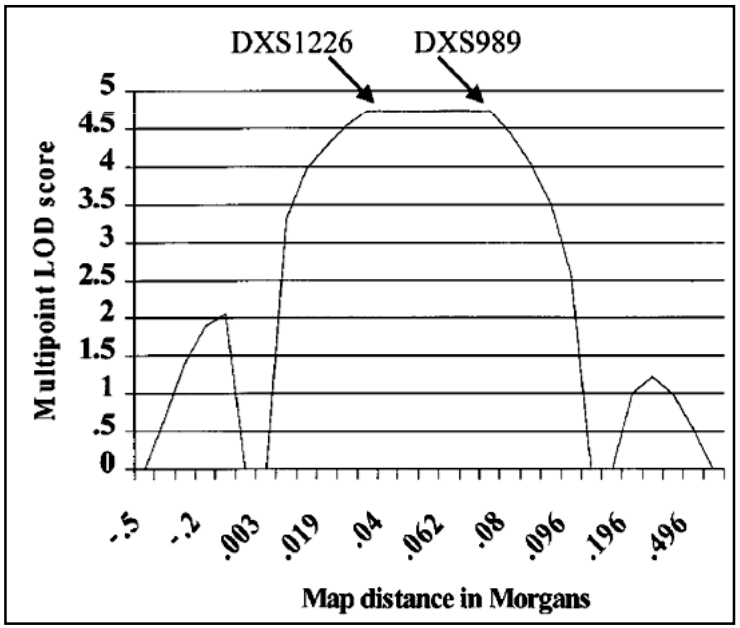
Am. J. Hum. Genet. 67:1004–1007, 2000

Report

Mapping a Dominant Form of Multinodular Goiter to Chromosome Xp22

F. Capon,[1] A. Tacconelli,[1] E. Giardina,[1] S. Sciacchitano,[2] R. Bruno,[3] V. Tassi,[4] V. Trischitta,[4] S Filetti,[5] B Dallapiccola,[2,6] and G. Novelli[1]





European Journal of Human Genetics (2000) 8, 809–812
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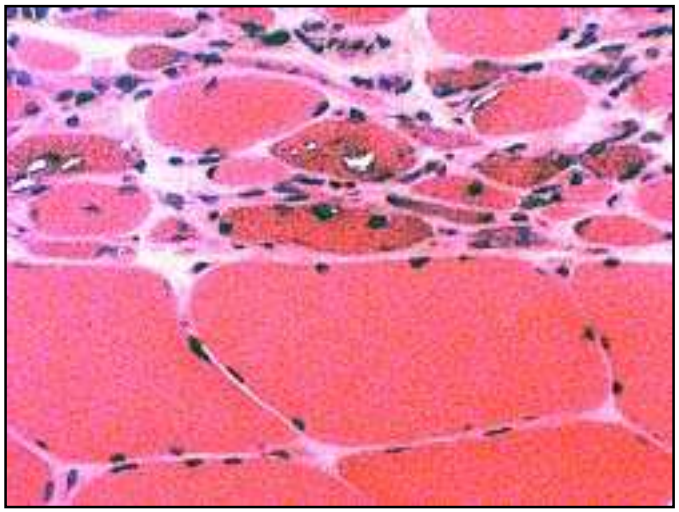
www.nature.com/ejhg

SHORT REPORT

Fine mapping of a distinctive autosomal dominant vacuolar neuromyopathy using 11 novel microsatellite markers from chromosome band 19p13.3

OMIM 601846

F Sangiuolo[1], E Bruscia[1], F Capon[1], S Servidei[2], B Dallapiccola[3] and G Novelli[1]



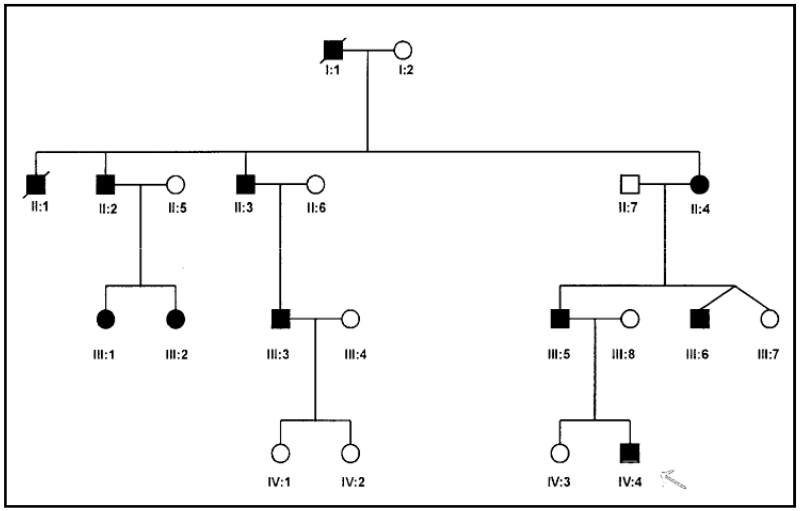


Table 2 Two-point lod score data generated by markers on 19p13.3

	Recombination fraction lod score						
Marker	*0.0*	*0.01*	*0.05*	*0.1*	*0.2*	*0.3*	*0.4*
27139 (TG)	–0.11	–0.10	–0.06	–0.04	–0.02	–0.01	–0.03
26529 (TA)	–6.5	–2.37	–1.03	–0.51	–0.1	–0.01	–0.04
30140 (GT)	1.67	1.64	1.49	1.31	0.934	0.564	0.24
28154 (ATT)	–1.34	0.40	0.93	1.02	0.88	0.6	0.28
335474 (CA)	–0.35	0.46	0.94	1.02	0.88	0.60	0.28
31646a (GA)	0.96	0.94	0.84	0.71	0.46	0.23	0.06
31646b (TAA)	–0.89	–0.13	0.37	0.50	0.47	0.32	0.14
34169 (TAAA)	2.99	2.93	2.71	2.40	1.78	1.12	0.46
34296 (CA)	1.44	1.41	1.29	1.12	0.80	0.46	0.15
30676 (TTTA)	1.44	1.41	1.29	1.12	0.80	0.46	0.15

Paraplegia spastica (SPG19 - OMIM 607052)

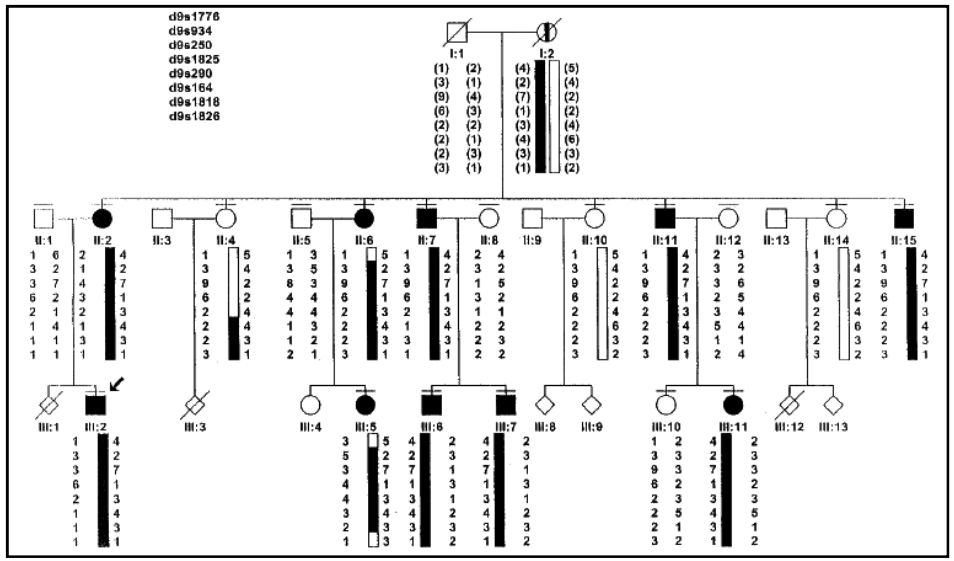
Novel Locus for Autosomal Dominant Pure Hereditary Spastic Paraplegia (SPG19) Maps to Chromosome 9q33–q34

Enza Maria Valente, MD,[1] Francesco Brancati, MD,[1,2] Viviana Caputo, BSc,[1] Enrico Bertini, MD,[3] Clarice Patrono, BSc,[3] Danilo Costanti, MD,[4] and Bruno Dallapiccola, MD[1,2]

Hereditary spastic paraplegia is a clinically and genetically heterogeneous disorder characterized by progressive spasticity of the lower limbs. Seven loci for autosomal dominant pure hereditary spastic paraplegia (ADPHSP) have already been mapped on chromosomes 14q, 2p, 15q, 8p, 12q, 19q, and 2q. We report on an Italian family affected by ADPHSP for which we excluded linkage with the known loci and performed a genome-wide search. Linkage analysis and haplotype construction permitted the identification of a novel ADPHSP locus on the long arm of chromosome 9, designated SPG19. The phenotype was characterized by late onset (range, 36–55 years) and mild disability, with only 1 patient bound to a wheelchair after 31 years of disease. Urinary disturbances (urgency and/or incontinence) were always present, even in young patients with a short disease history.

Ann Neurol 2002;51:681–685





Sordità genetica

European Journal of Human Genetics (2001) 9, 667–671
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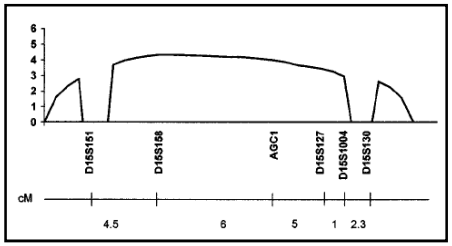
www.nature.com/ejhg

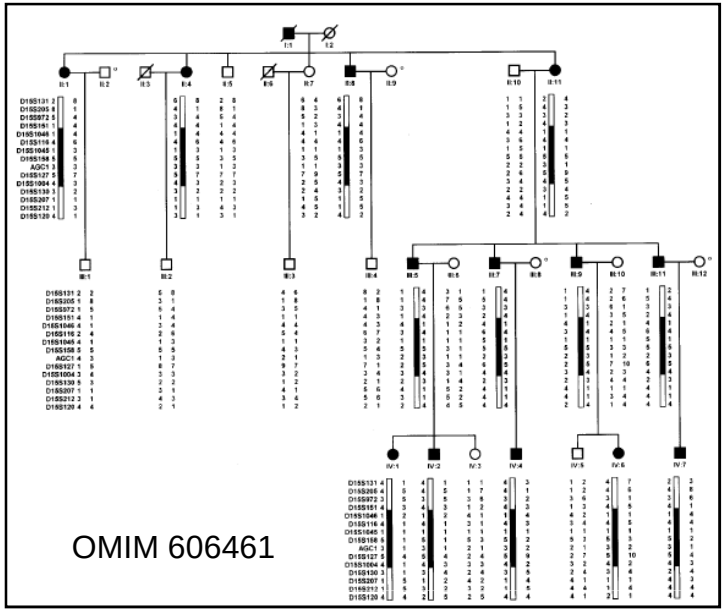
ARTICLE

Mapping of a new autosomal dominant nonsyndromic hearing loss locus (DFNA30) to chromosome 15q25-26

Massimo Mangino[1], Elisabetta Flex[1], Francesca Capon[2], Federica Sangiuolo[2], Edoardo Carraro[3], Francesca Gualandi[4], Manuela Mazzoli[3], Alessandro Martini[3], Giuseppe Novelli*[,2] and Bruno Dallapiccola[1]





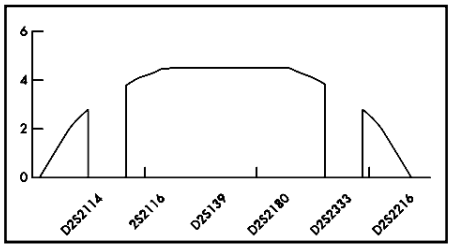


OMIM 606461

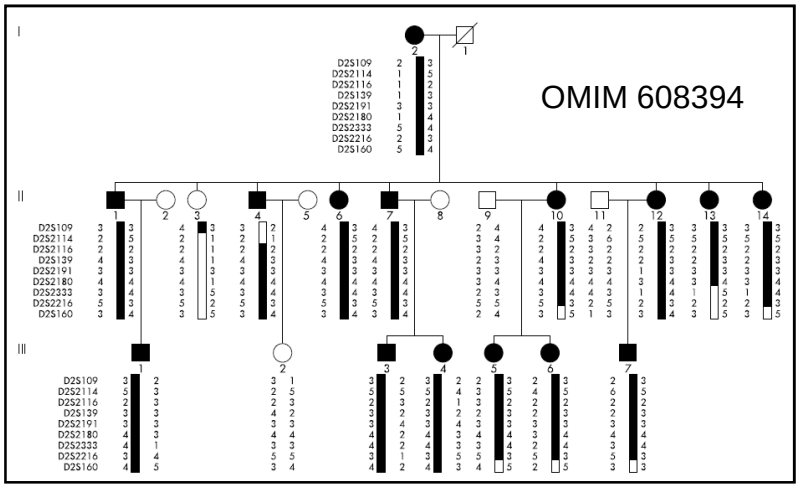
Mapping of a new autosomal dominant non-syndromic hearing loss locus (DFNA43) to chromosome 2p12

E Flex, M Mangino, M Mazzoli, A Martini, V Migliosi, A Colosimo, R Mingarelli, A Pizzuti, B Dallapiccola

J Med Genet 2003;**40**:278–282

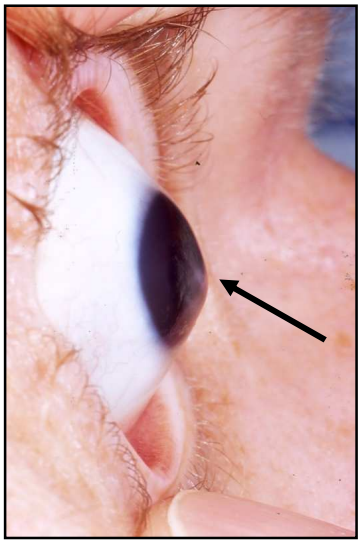






OMIM 608394

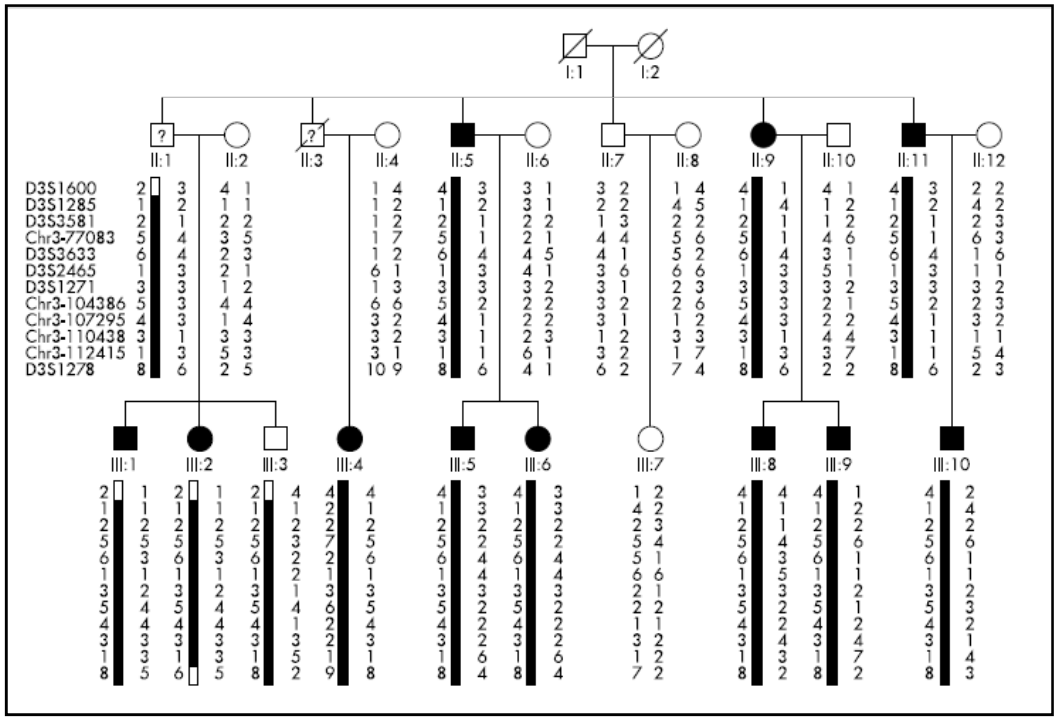
Cheratocono (KTCN3 – OMIM 608586)



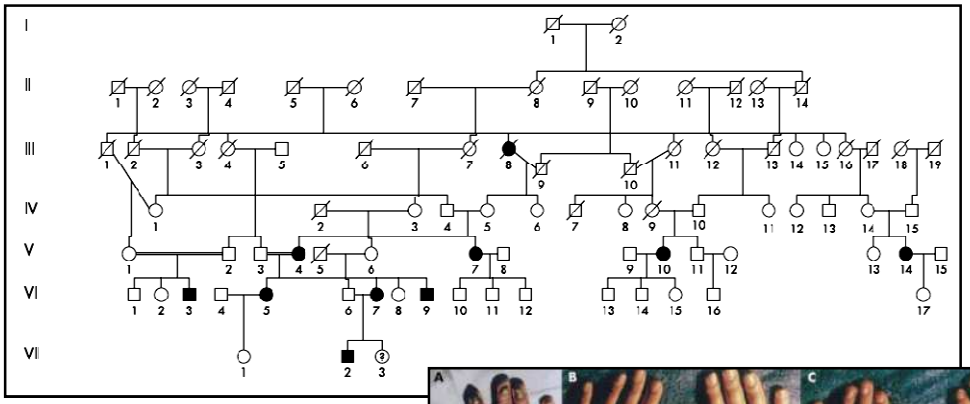
A locus for autosomal dominant keratoconus maps to human chromosome 3p14–q13

F Brancati, E M Valente, A Sarkozy, J Fehèr, M Castori, P Del Duca, R Mingarelli, A Pizzuti, B Dallapiccola

J Med Genet 2004;**41**:188–192. doi: 10.1136/jmg.2003.012872



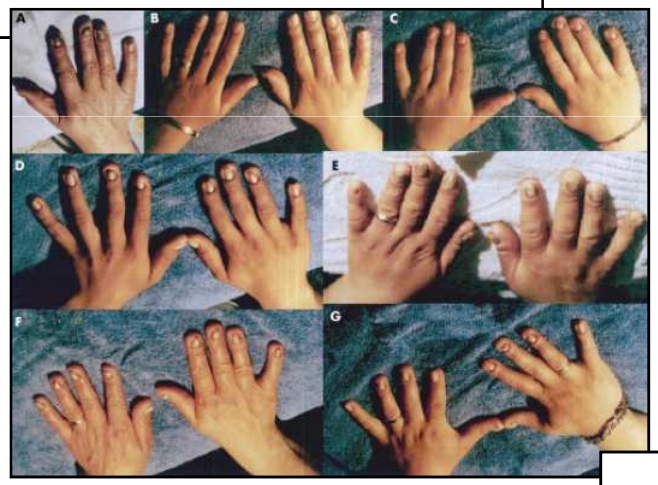
Candidiasi ungueale familiare cronica con deficit di ICAM1 [CD54] (CANDF4 - OMIM 613108)



Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis

D Zuccarello*, D C Salpietro*, S Gangemi, V Toscano, M V Merlino, S Briuglia, G Bisignano, M Mangino, R Mingarelli, B Dallapiccola

J Med Genet 2002;**39**:671–675





European Journal of Human Genetics (2003) 11, 433–436
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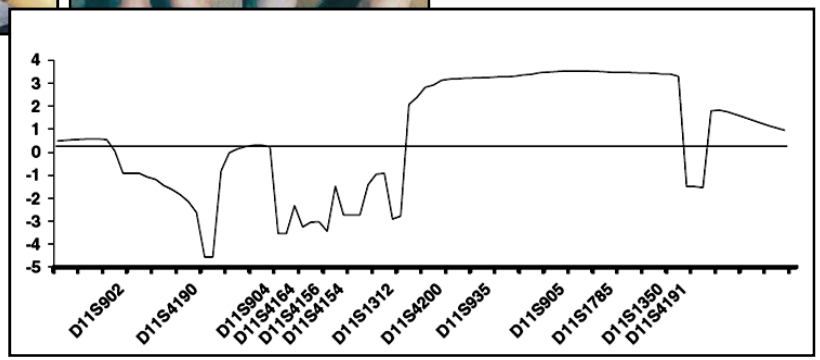
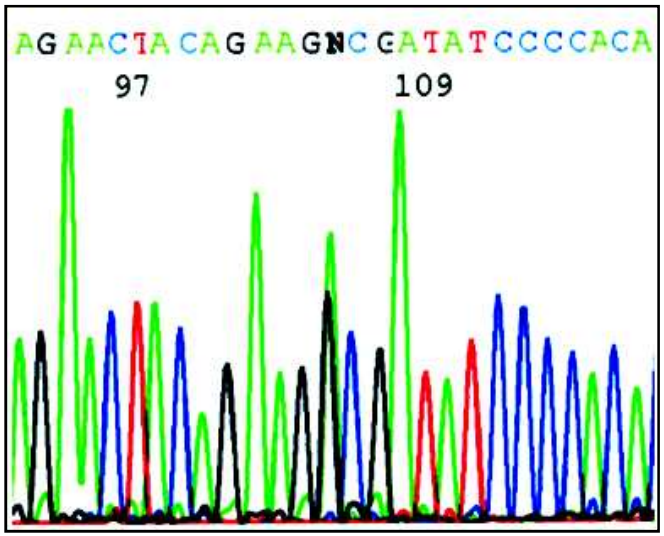
www.nature.com/ejhg

ARTICLE

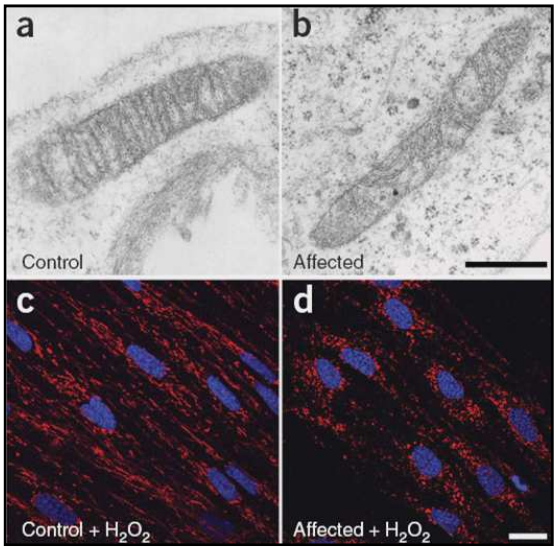
A gene for familial isolated chronic nail candidiasis maps to chromosome 11p12–q12.1

M Mangino*[,1], DC Salpietro[2], D Zuccarello[1,3], S Gangemi[4], L Rigoli[2], MV Merlino[2], S Briuglia[2], G Bisignano[5], R Mingarelli[1,3] and B Dallapiccola[1,3]





Identificazione di geni-malattia





nature genetics • volume 24 • march 2000

Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis

Victor L. Ruiz-Perez[1*], Susan E. Ide[2,5*], Tim M. Strom[3*], Bettina Lorenz[3], David Wilson[1], Kathryn Woods[1], Lynn King[4], Clair Francomano[4], Peter Freisinger[6], Stephanie Spranger[7], Bruno Marino[8], Bruno Dallapiccola[9], Michael Wright[1], Thomas Meitinger[3], Mihael H. Polymeropoulos[2] & Judith Goodship[1]

OMIM 225500





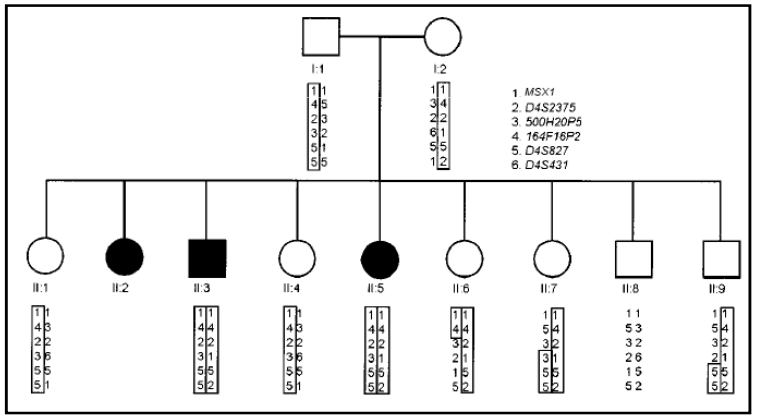


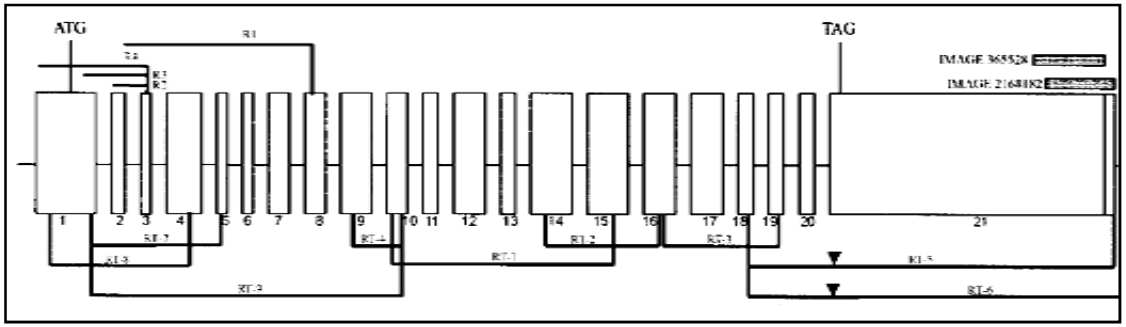












Sindrome osteoporosi-pseudoglioma (OMIM259770)

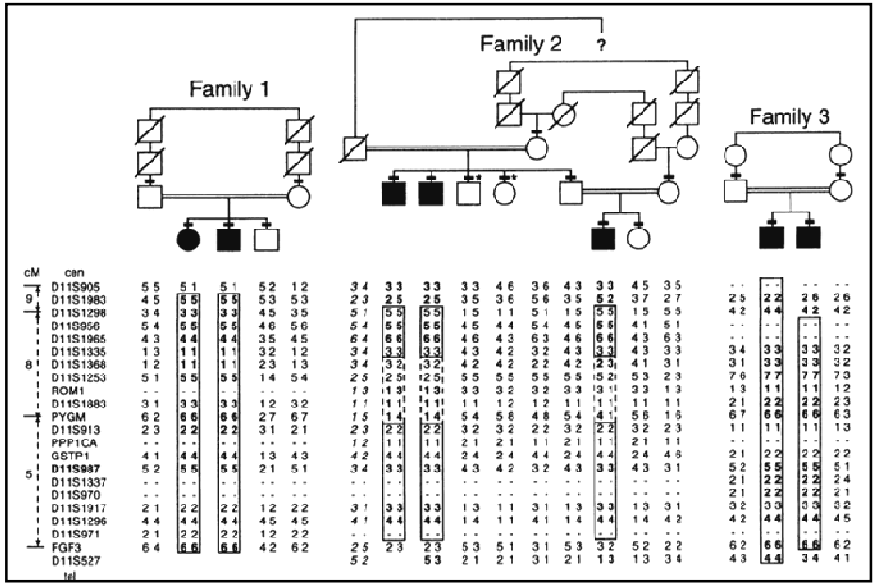
Cell, Vol. 107, 513–523, November 16, 2001, Copyright ©2001 by Cell Press

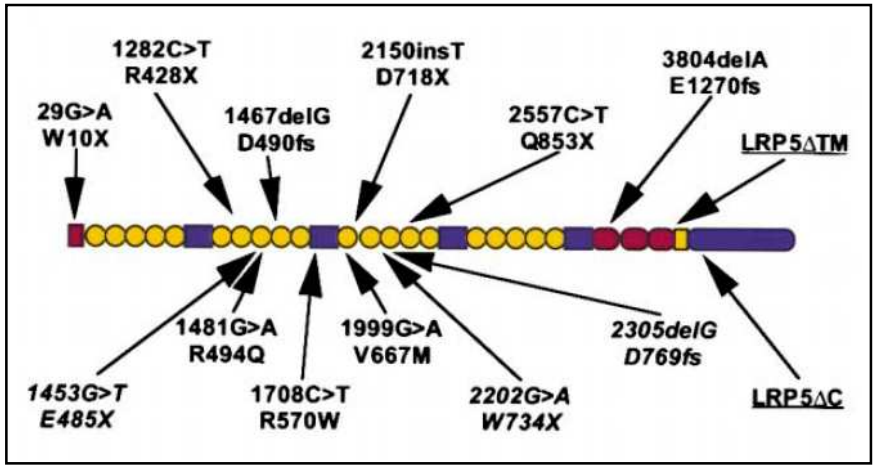
LDL Receptor-Related Protein 5 (LRP5) Affects Bone Accrual and Eye Development

Yaoqin Gong,[2] Roger B. Slee,[2] Naomi Fukai, Georges Rawadi, Sergio Roman-Roman, Anthony M. Reginato, Hongwei Wang, Tim Cundy, Francis H. Glorieux, Dorit Lev, Margaret Zacharin, Konrad Oexle, Jose Marcelino, Wafaa Suwairi, Shauna Heeger, George Sabatakos, Suneel Apte, William N. Adkins, Jeremy Allgrove, Mine Arslan-Kirchner, Jennifer A. Batch, Peter Beighton, Graeme C. M. Black, Richard G. Boles, Laurence M. Boon, Carla Borrone, Han G. Brunner, Georges F. Carle, Bruno Dallapiccola, Anne De Paepe, Barbara Floege, Melissa Lees Halfhide, Bryan Hall, Raoul C. Hennekam, Tatsuo Hirose, Ab Jans, Harald Jüppner, Chong Ae Kim, Kim Keppler-Noreuil, Alfried Kohlschuetter, Didier LaCombe, Marie Lambert, Emmanuelle Lemyre, Tom Letteboer, Leena Peltonen, Rajkumar S. Ramesar, Marta Romanengo, Hannu Somer, Elisabeth Steichen-Gersdorf, Beat Steinmann, Beth Sullivan, Andrea Superti-Furga, Walter Swoboda, Marie-José van den Boogaard, Wim Van Hul, Miikka Vikkula, Marcela Votruba, Bernhard Zabel, Teresa Garcia, Roland Baron, Bjorn R. Olsen, and Matthew L. Warman[1]
The Osteoporosis-Pseudoglioma Syndrome Collaborative Group[3]







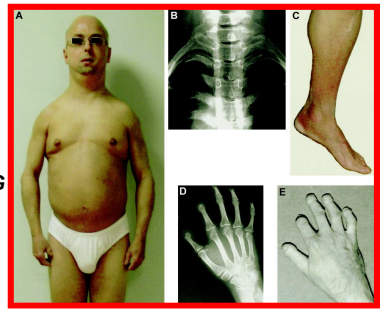


Definizione dei fenotipi clinici associati alla mutazioni alleliche di *LAMNA*



Progeria di Hutchinson Gilford (HGPS

OMIM
248370
Novelli et al.AJHG 71:426-31, 2002



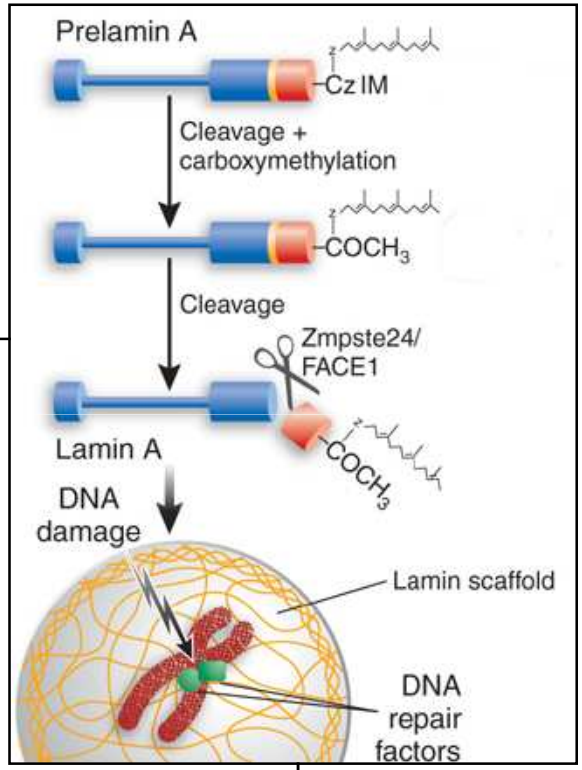
Displasia mandibulo-acrale (MAD)



Lipodistrofia familiare parziale (FPLD2)

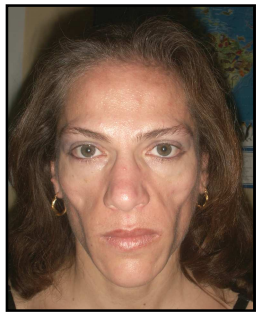


Dermopatia restrittiva (RD)

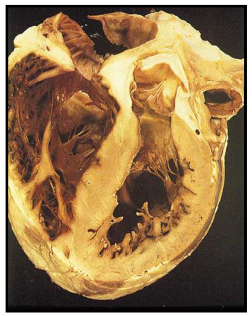




Distrofia dei cingoli tipo 1B (LGMD1B)



Lipodistrofia, diabete insulino-resistente
steatosi epatica, papule leucomelanodermiche



Cardiomiopatia dilatativa tipo 1° (CMD1A)



Malattia di Charcot-Marie-Tooth, tipo 2B! (CMT2B1)

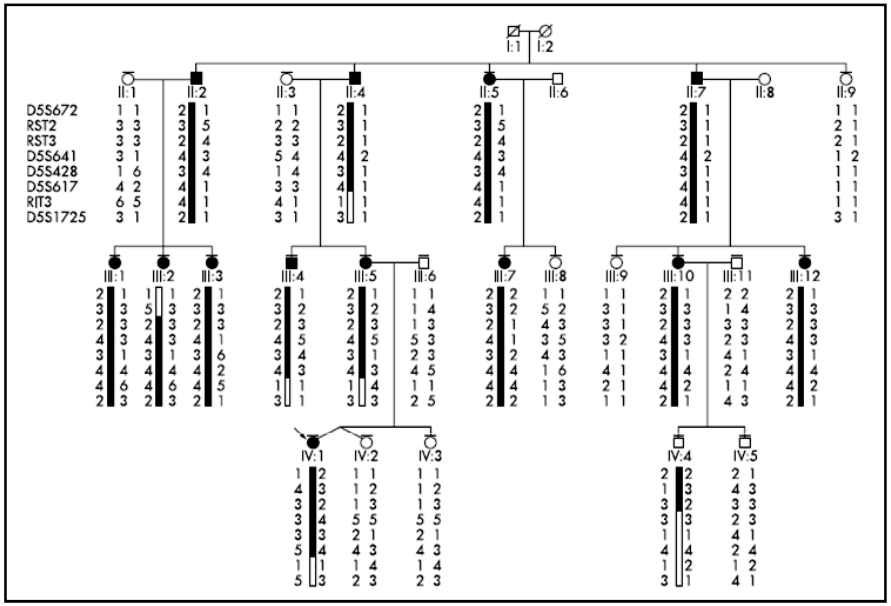


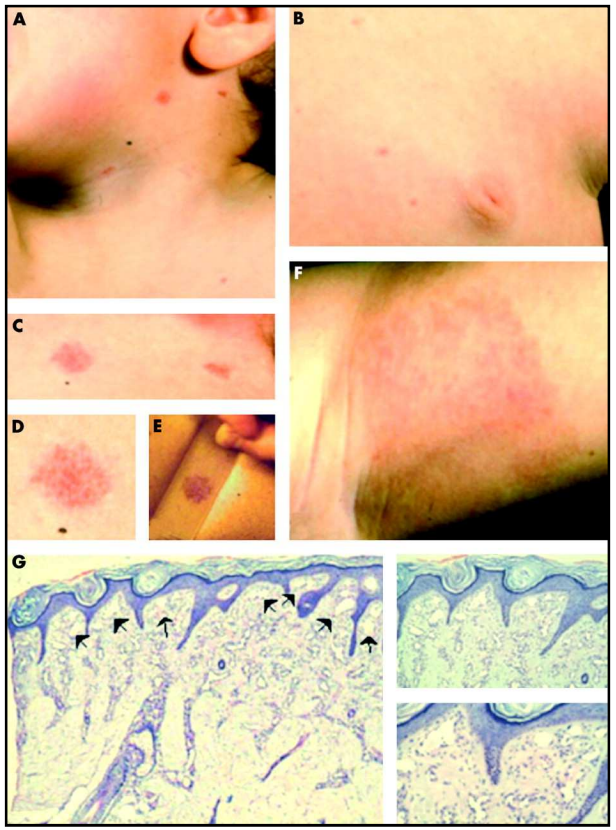
Distrofia muscolare di Emery-Dreyfuss, tipo 2 (EDMD2)

Autosomal dominant hereditary benign telangiectasia maps to the *CMC1* locus for capillary malformation on chromosome 5q14

F Brancati, E M Valente, G Tadini, V Caputo, A Di Benedetto, C Gelmetti, B Dallapiccola

J Med Genet 2003;**40**:849–853



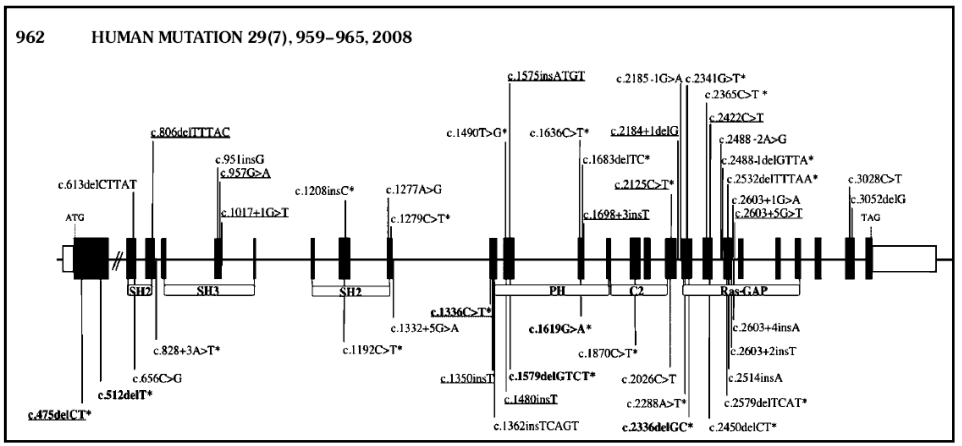


HUMAN MUTATION 29(7), 959–965, 2008

RESEARCH ARTICLE

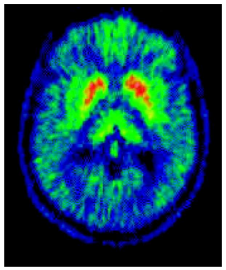
Parkes Weber Syndrome, Vein of Galen Aneurysmal Malformation, and Other Fast-Flow Vascular Anomalies Are Caused by *RASA1* Mutations

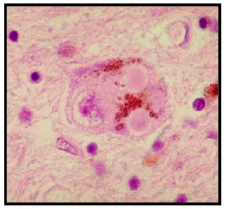
Nicole Revencu,[1,2] Laurence M. Boon,[1-3] John B. Mulliken,[4] Odile Enjolras,[5] Maria Rosa Cordisco,[6] Patricia E. Burrows,[4] Philippe Clapuyt,[7] Frank Hammer,[7] Josée Dubois,[8] Eulalia Baselga,[9] Francesco Brancati,[10] Robin Carder,[11] José Miguel Ceballos Quintal,[12] Bruno Dallapiccola,[10] Gayle Fischer,[13] Ilona J. Frieden,[14] Maria Garzon,[15] John Harper,[16] Jennifer Johnson-Patel,[17] Christine Labrèze,[18] Loreto Martorell,[19] Harriet J. Paltiel,[4] Annette Pohl,[20] Julie Prendiville,[21] Isabelle Quere,[22] Dawn H. Siegel,[14] Enza Maria Valente,[10] Annet Van Hagen,[23] Liselot Van Hest,[23] Keith K. Vaux,[24] Asuncion Vicente,[25] Lisa Weibel,[16] David Chitayat,[26] and Miikka Vikkula[1*]



RAS p21 protein activator (Guanosine Triphosphatase ActivatingPprotein – GAP)

Malattia di Parkinson giovanile autosomica recessiva (OMIM 605909)

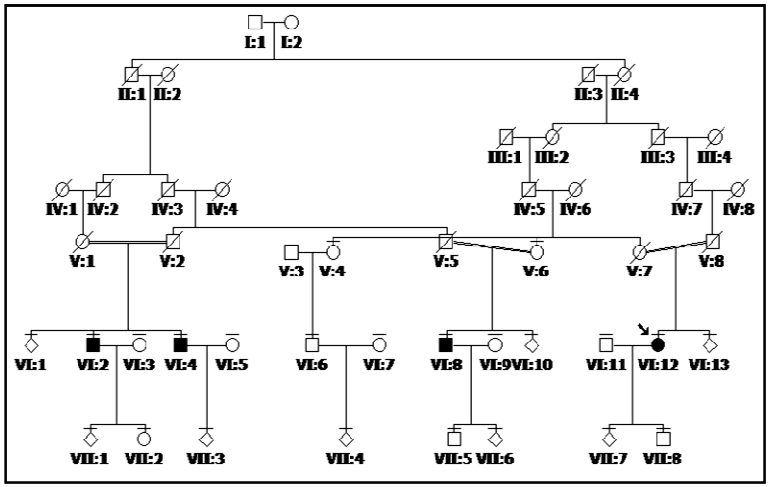


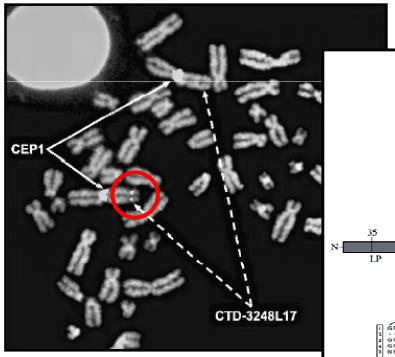


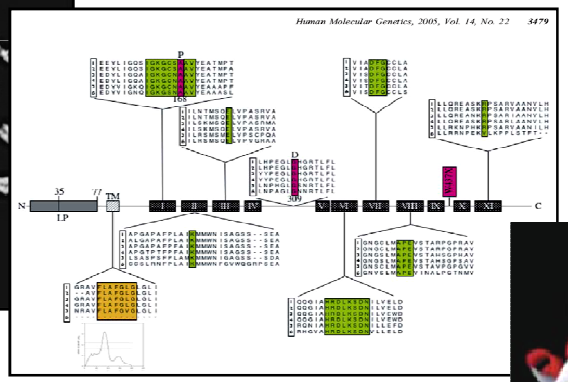
Hereditary Early-Onset Parkinson's Disease Caused by Mutations in *PINK1*

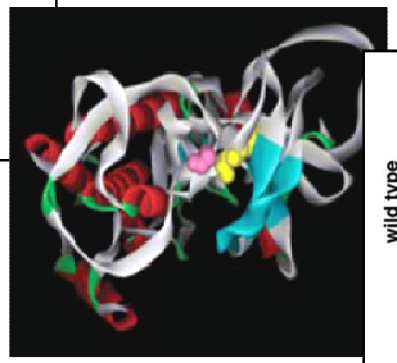
Enza Maria Valente,[1]*‡ Patrick M. Abou-Sleiman,[2]* Viviana Caputo,[1,3]† Miratul M. K. Muqit,[2,4]† Kirsten Harvey,[5] Suzana Gispert,[6] Zeeshan Ali,[6] Domenico Del Turco,[7] Anna Rita Bentivoglio,[9] Daniel G Healy,[2] Alberto Albanese,[10] Robert Nussbaum,[11] Rafael González-Maldonado,[12] Thomas Deller,[7] Sergio Salvi,[1] Pietro Cortelli,[13] William P. Gilks,[2] David S. Latchman,[4,14] Robert J. Harvey,[5] Bruno Dallapiccola,[1,3] Georg Auburger,[8]‡ Nicholas W. Wood[2]‡

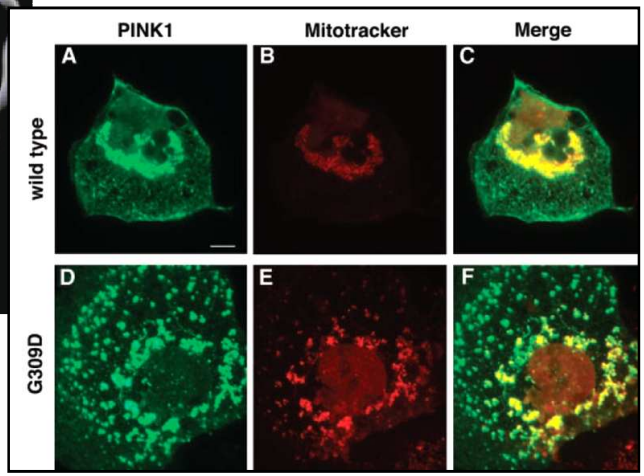
21 MAY 2004 VOL 304 SCIENCE www.sciencemag.org



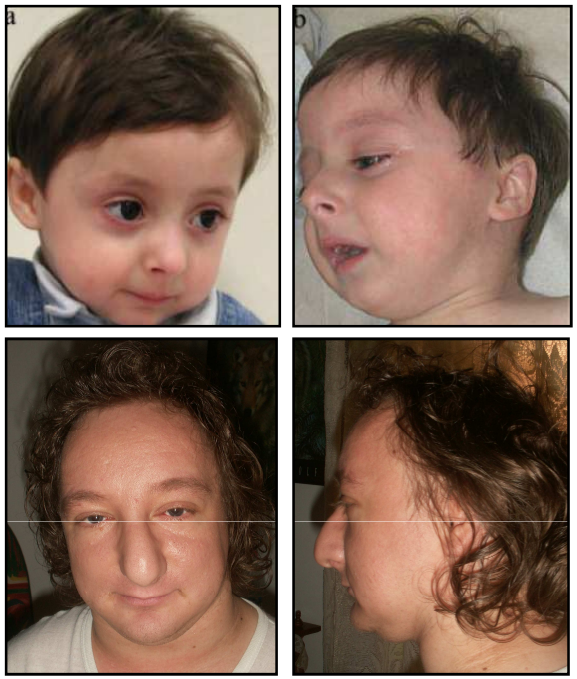








Identificazione del gene del nanismo primitivo osteodisplastico microcefalico, tipo II (MOPDII – OMIM, 210720 – *PCNT2* – 21q22)



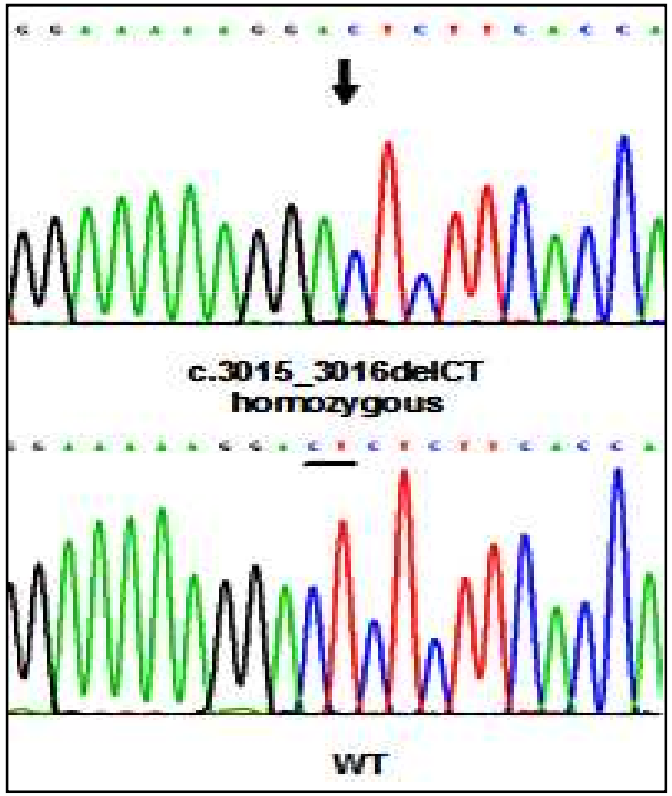


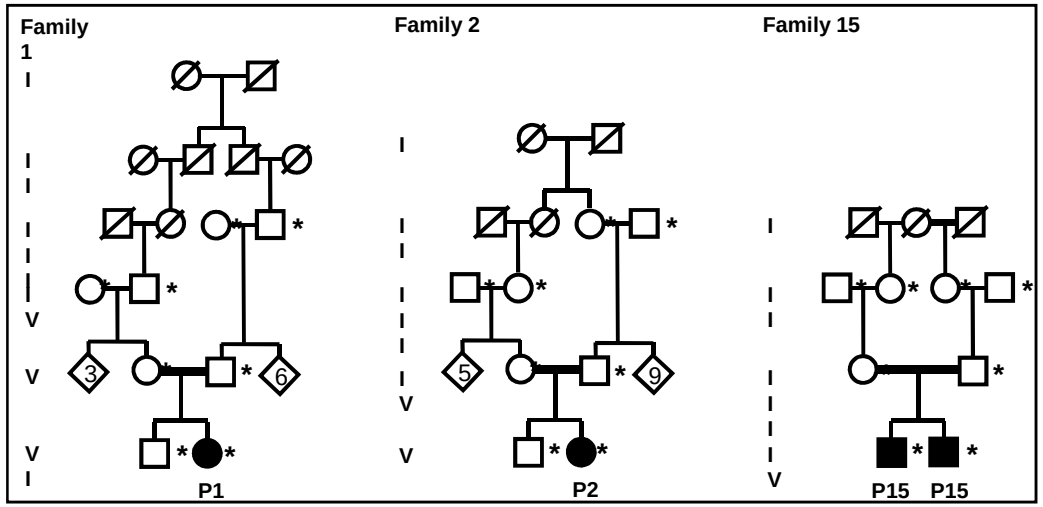
American Journal of Medical Genetics 139A:212–215 (2005)

Clinical Report

Majewski Osteodysplastic Primordial Dwarfism Type II (MOPD II) Complicated by Stroke: Clinical Report and Review of Cerebral Vascular Anomalies

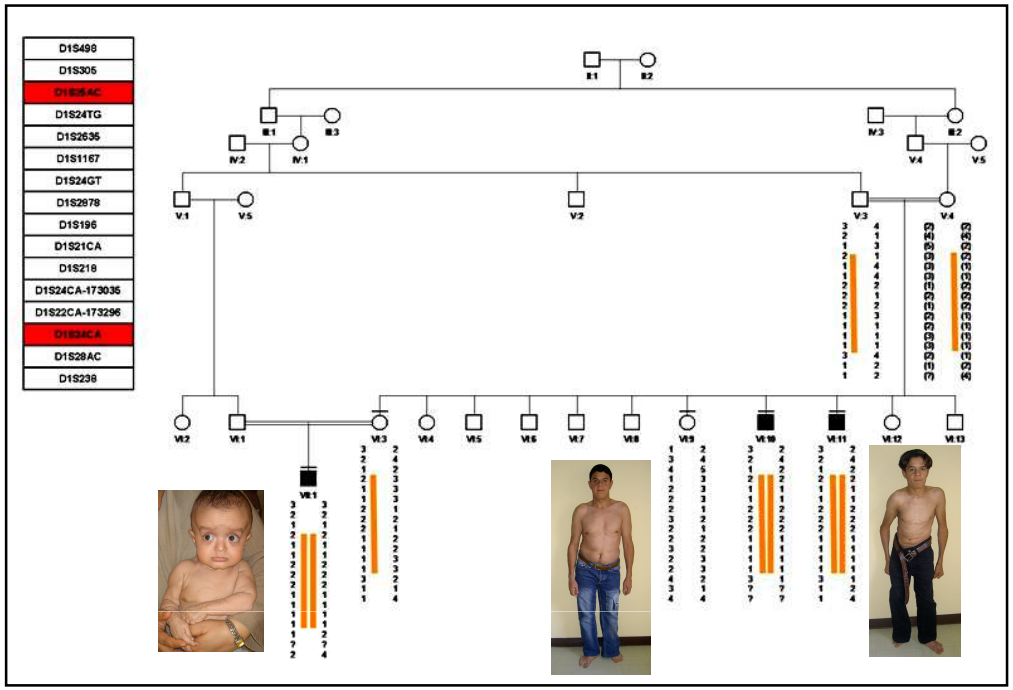
Francesco Brancati,[1,2,3] Marco Castori,[2,3] Rita Mingarelli,[3] and Bruno Dallapiccola[2,3]*

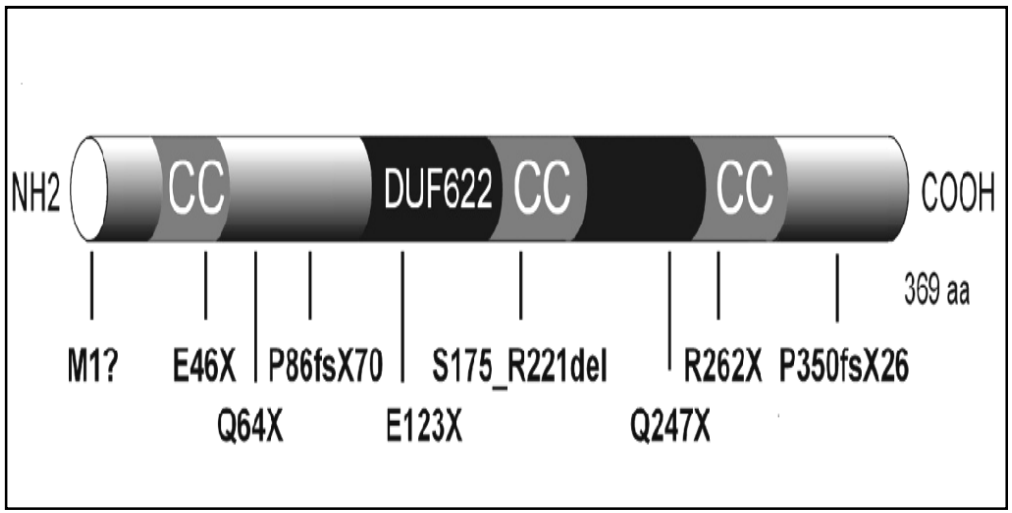


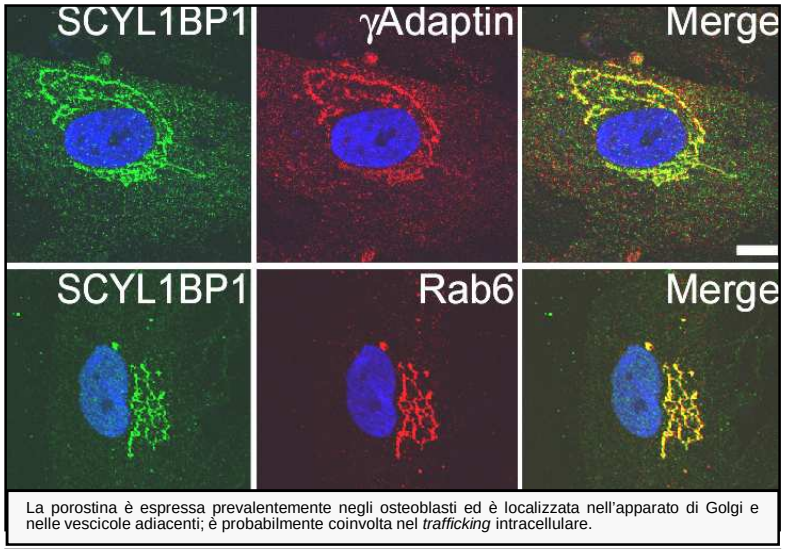


Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB, van Essen AJ, Goecke TO, Al-Gazali L, Chrzanowska KH, Zweier C, Brunner HG, Becker K, Curry CJ, Dallapiccola B, Devriendt K, Dörfler A, Kinning E, Megarbane A, Meinecke P, Semple RK, Spranger S, Toutain A, Trembath RC, Voss E, Wilson L, Hennekam R, de Zegher F, Dörr HG, Reis A: Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. Science, 319:816-9, 2008.

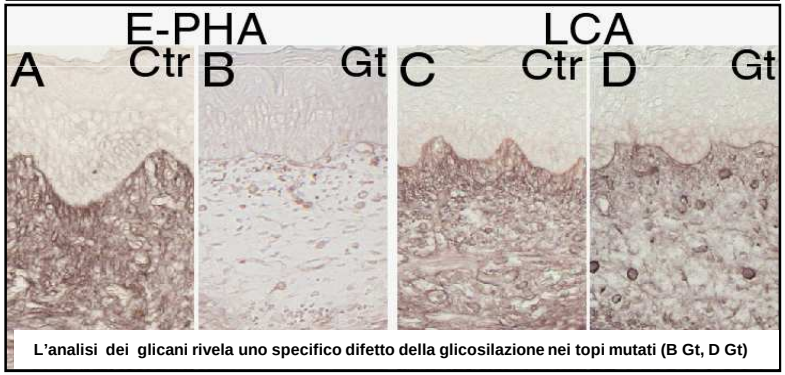
Geroderma osteodisplasticum:mappatura e clonaggio del gene-malattia (OMIM231070)



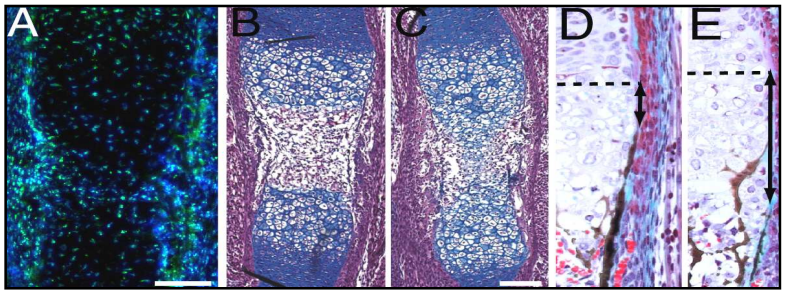




La porostina è espressa prevalentemente negli osteoblasti ed è localizzata nell'apparato di Golgi e nelle vescicole adiacenti; è probabilmente coinvolta nel *trafficking* intracellulare.

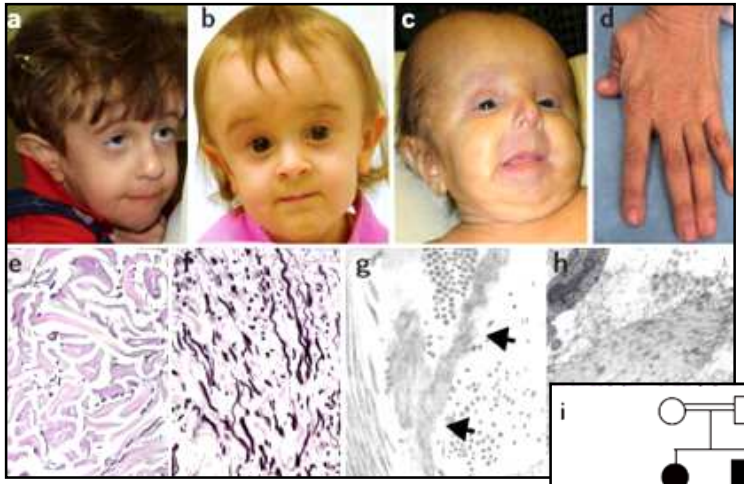


L'analisi dei glicani rivela uno specifico difetto della glicosilazione nei topi mutati (B Gt, D Gt)

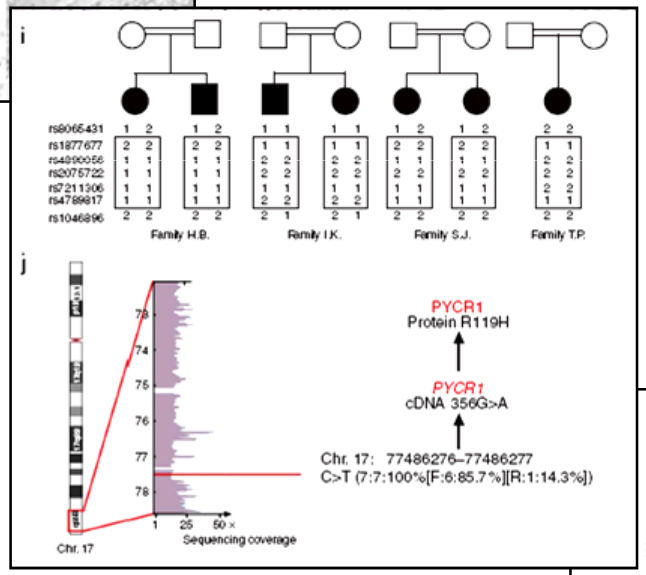


Hennies HC, Kornak U, Zhang H, Egerer J, Zhang X, Seifert W, Kühnisch J, Budde B, Nätebus M, Brancati F, Wilcox WR, Müller D, Kaplan PB, Rajab A, Zampino G, Fodale V, Dallapiccola B, Newman W, Metcalfe K, Clayton-Smith J, Tassabehji M, Steinmann B, Barr FA, Nürnberg P, Wieacker P, Mundlos S: Gerodermia osteodysplastic is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. Nat Genet, 40:1410-2, 2008.

Cutis laxa, tipo IIB, autosomica recessiva (OMIM 612940): mappatura e clonaggio del gene-malattia *PYCR*1 in 17q25.3



a. Wrinkly skin syndrome (OMIM 278250)
b. Gerodermia osteodyplastica (OMIM 231070)
c. De Barsey syndrome (OMIM 219150)



Mutations in *PYCR1* cause cutis laxa with progeroid features

Bruno Reversade[1,33], Nathalie Escande-Beillard[1,33], Aikaterini Dimopoulou[2], Björn Fischer[2], Serene C Chng[1], Yun Li[3], Mohammad Shboul[1], Puay-Yoke Tham[1], Hülya Kayserili[4], Lihadh Al-Gazali[5], Monzer Shahwan[6], Francesco Brancati[7,8], Hane Lee[9], Brian D O'Connor[9], Mareen Schmidt-von Kegler[2,10], Barry Merriman[9], Stanley F Nelson[9], Amira Masri[11], Fawaz Alkazaleh[11], Deanna Guerra[12], Paola Ferrari[13], Arti Nanda[14], Anna Rajab[15], David Markie[16], Mary Gray[16], John Nelson[17], Arthur Grix[18], Annemarie Sommer[19], Ravi Savarirayan[20], Andreas R Janecke[21], Elisabeth Steichen[22], David Sillence[23], Ingrid Hausser[24], Birgit Budde[25], Gudrun Nürnberg[25], Peter Nürnberg[25], Petra Scemann[10,26], Désirée Kunkel[26], Giovanna Zambruno[27], Bruno Dallapiccola[7], Markus Schuelke[28], Stephen Robertson[29], Hanan Hamamy[6], Bernd Wollnik[3,30,31], Lionel Van Maldergem[32], Stefan Mundlos[2,10,26] & Uwe Kornak[2,10]

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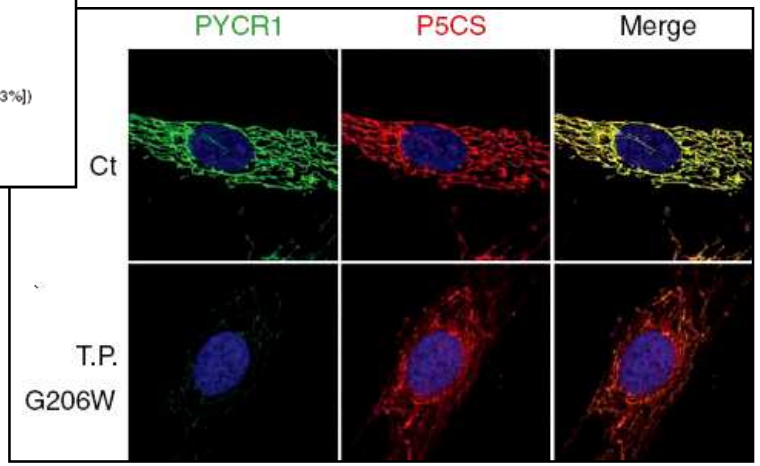


Identificazione di mutazioni di geni della cascata di RAS-MAPK in pazienti con sottotipi clinici della sindrome di Noonan (OMIM 163950)



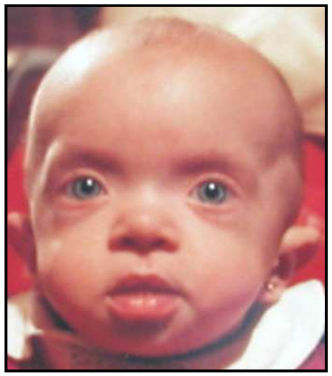
sindrome di Noonan
PTPN11 *ex 3*
forma classica

NS1 (OMIM 163950)



sindrome LEOPARD
PTPN11 *ex 12*
lentiggini, cardiomiopatia

LS1 (OMIM 151100)



sindrome Noonan-like
PTPN11 *ex 13*
cherubinismo, sinovite poliarticolare villonodulare
(OMIM 163955)



sindrome di Noonan
NRAS

(OMIM 164790)



sindrome di Noonan
KRAS
grave

NS3 (OMIM 609942)



sindrome di Noonan

SHOC2
"loose anagen hair"
(OMIM 607721)



sindrome di Noonan

SOS1
lieve, statura normale
NS4 (OMIM 610733)



sindrome di Noonan

RAF1
cardiomiopatia
NS5 (OMIM 611553)
LS2 (OMIM 611554)



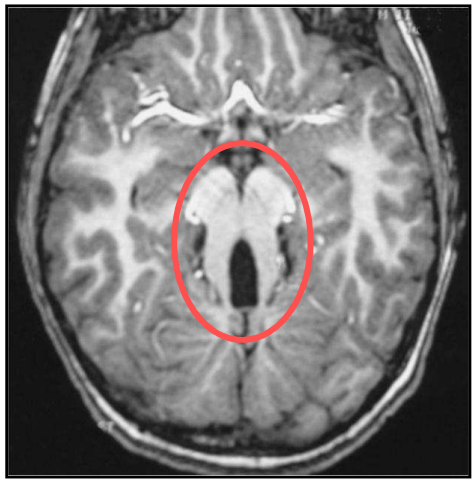
sindrome di Noonan

BRAF
simil-CFCS
(OMIM 115150)

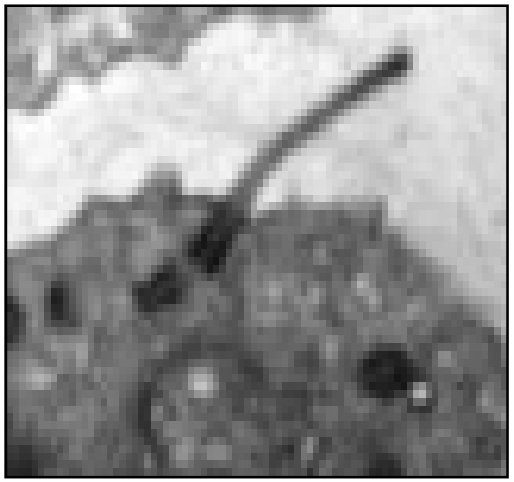


sindrome Neurofibromatosi-Noonan
NF1
NF1 lieve
(OMIM 601321)

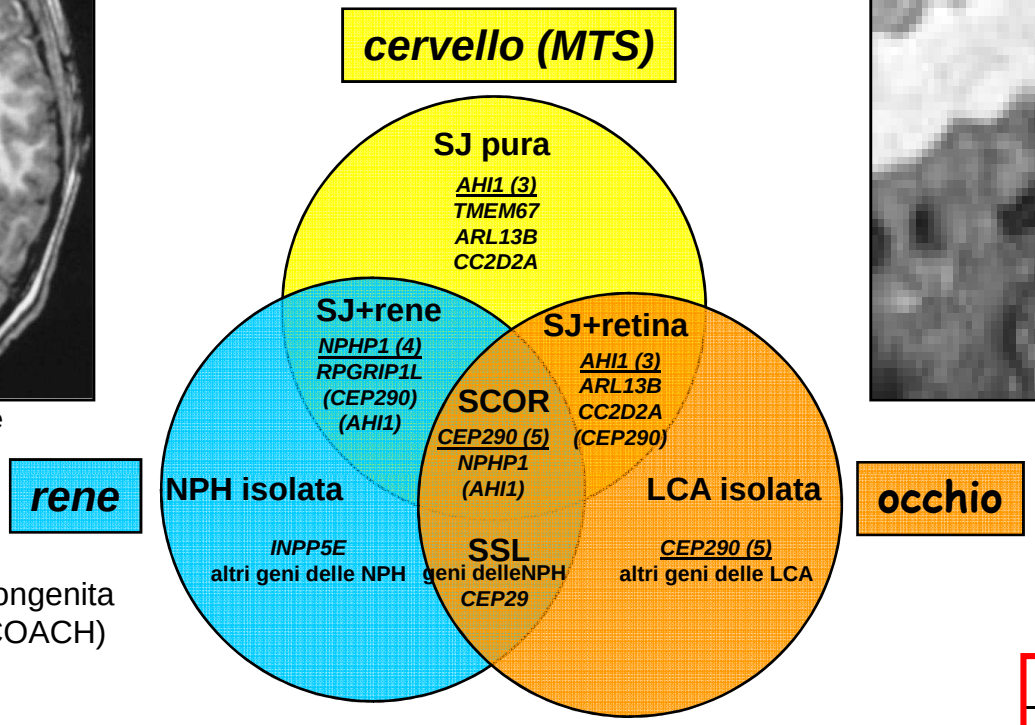
Identificazione della basi biologiche della sindrome di Joubert e delle sindromi correlate al segno del dente molare (OMIM 213300)



segno del dente molare



cilio primario

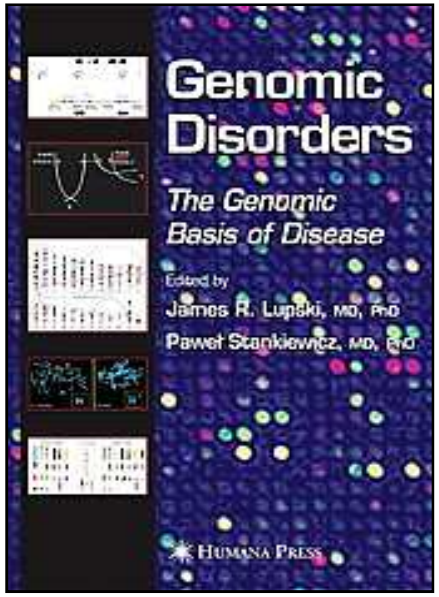


SJ + fibrosi epatica congenita
± colobomi oculari (COACH)
TMEM67 (6, ~60%)

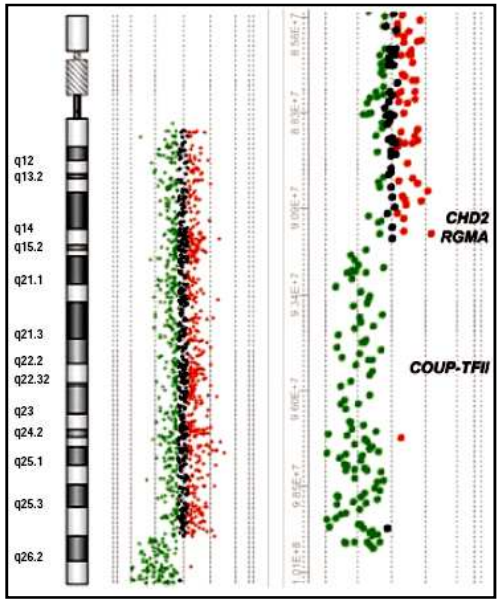
JBTS1	*INPP5E*
JBTS2	
JBTS3	*AHI1*
JBTS4	*NPHP1*
JBTS5	*CEP290*
JBTS6	*TMEM67*
JBTS7	*RPGRIP1L*
JBTS8	*ARL13B*
JBTS9	*CC2D2A*

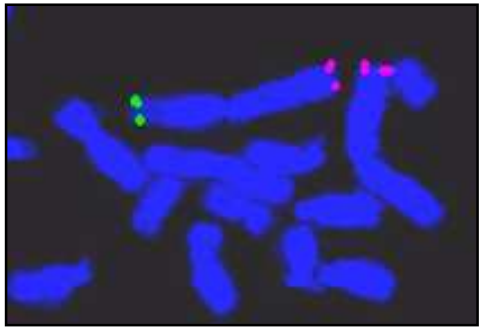
Valente EM, Silhavy JL, Brancati F, Barrano G, Krishnaswami SR, Castori M, Lancaster MA, Boltshauser E, Boccone L, Al-Gazali L, Fazzi E, Signorini S, Louie CM, Bellacchio E; International Joubert Syndrome Related Disorders Study Group, Bertini E, Dallapiccola B, Gleeson JG: Mutations in CEP290, which encodes a centrosomal protein, causes phenotypic forms of Joubert syndrome. Nat Genet, 38:623-5, 2006.

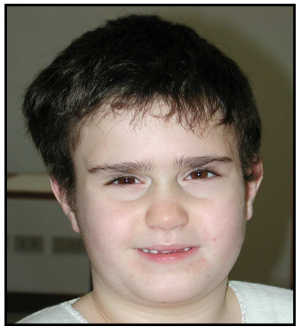
Bielas SL, Silhavy JL, Brancati F, Kisseleva MV, Al-Gazali L, Sztriha L, Bayoumi RA, Zaki MS, Abdel-Aleem A, Rosti RO, Kayserili H, Swistun D, Scott LC, Bertini E, Boltshauser E, Fazzi E, Travaglini L, Field SJ, Gayral S, Jacoby M, Schurmans S, Dallapiccola B, Majerus PW, Valente EM, Gleeson JG: Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. Nat Genet, 41:1032-6, 2009.



Identificazione di nuove sindromi genomiche

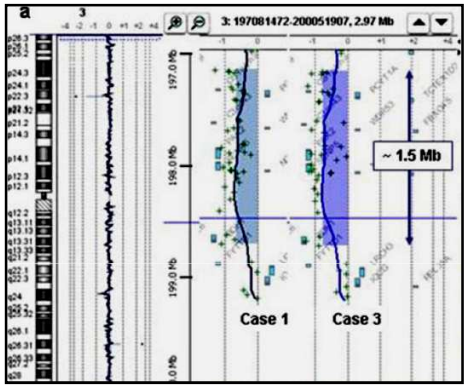


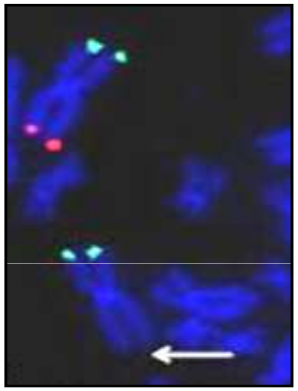




del 1p36
OMIM 607872

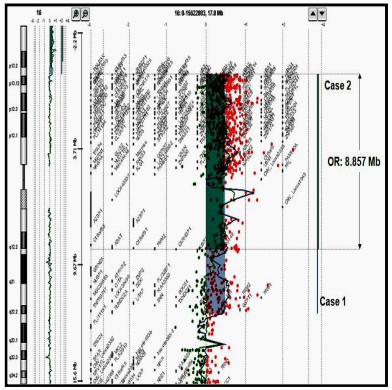
Battaglia A , Hoyme HE , Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, Bahi-Buisson N, Romano C, Williams CA, Brailey LL, Braley LL, Zuberi SM, Carey JC: Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics, 121: 404-10, 2008.

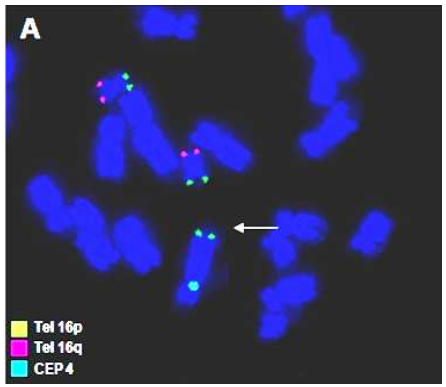





del 3q29
OMIM 609425

Digilio MC, Bernardini L, Mingarelli R, Capolino R, Capalbo A, Giuffrida MG, Versacci P, Novelli A, Dallapiccola B: 3q29 microdeletion: a mental retardation disorder unassociated with a recognizable phenotype in two mother-daughters pairs. Am J Med Genet, 149A:1777-81, 2009.

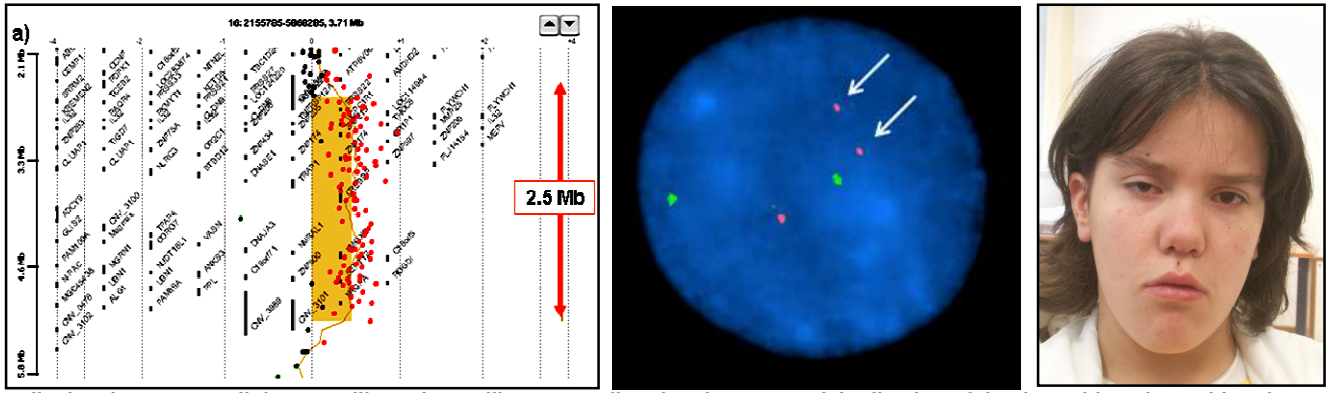






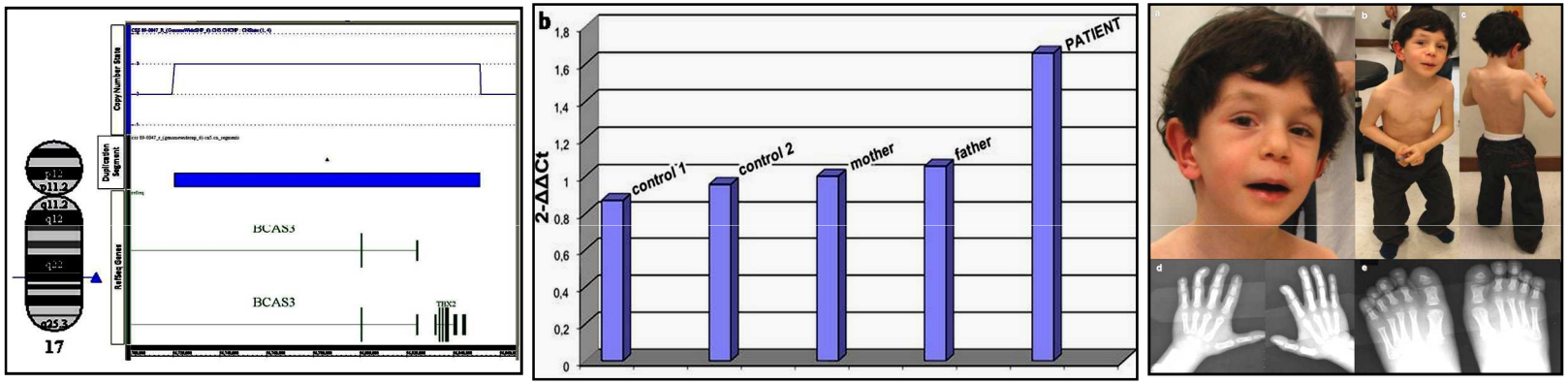

dup 16p13

Digilio MC, Bernardini L, Capalbo A, Capolino R, Gagliardi MG, Marino B, Novelli A, Dallapiccola B: 16p subtelomeric duplication: a clinically recognizable syndrome. . Eur J Hum Genet. 17:1135-40, 2009.



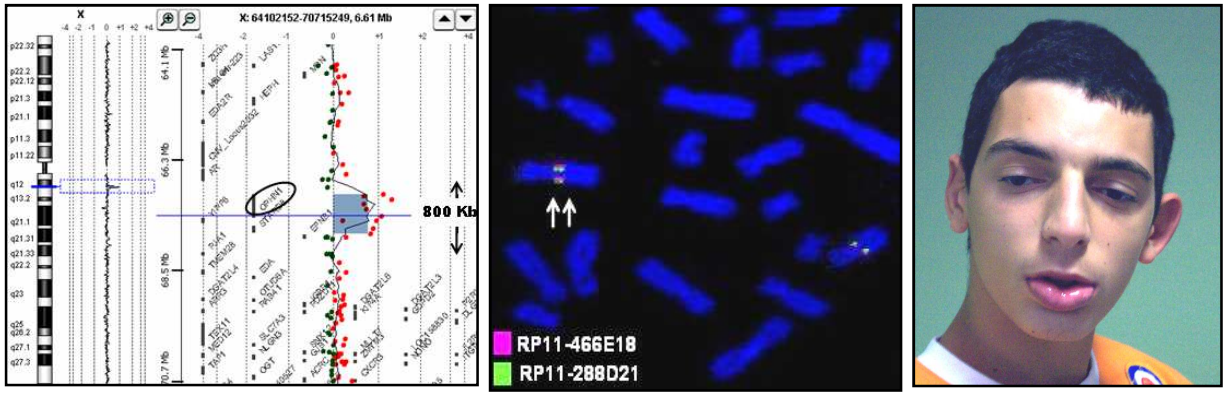
dup 16p13.3

Dallapiccola B, Bernardini L, Novelli A, Mingarelli R: Expanding the phenotype of duplication of the the Rubinstein-Taybi region on 16p13.3. Am J Med Genet A. 2009 Nov 16. [Epub ahead of print].



dup 17q23.2
(TBX2)

Radio FC, Bernardini L, Loddo S, Bottillo I, Novelli A, Mingarelli R, Dallapiccola B: TBX2 gene duplication associated with complex heart defect and skeletal malformations mimicking animal models heterozygous for TBX2 loss of function mutations. Hum Genet (in press)

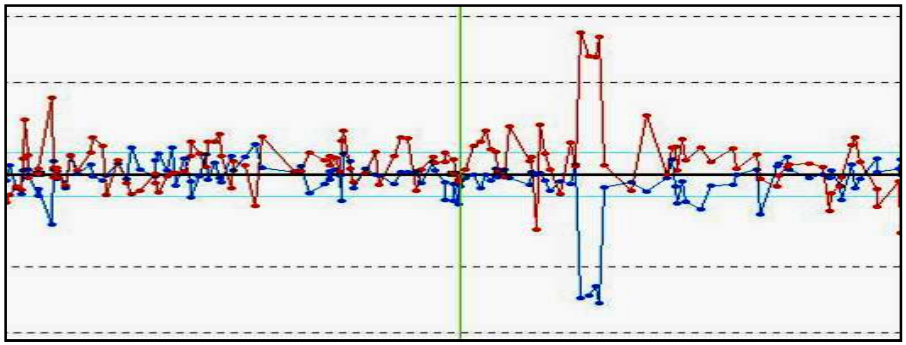


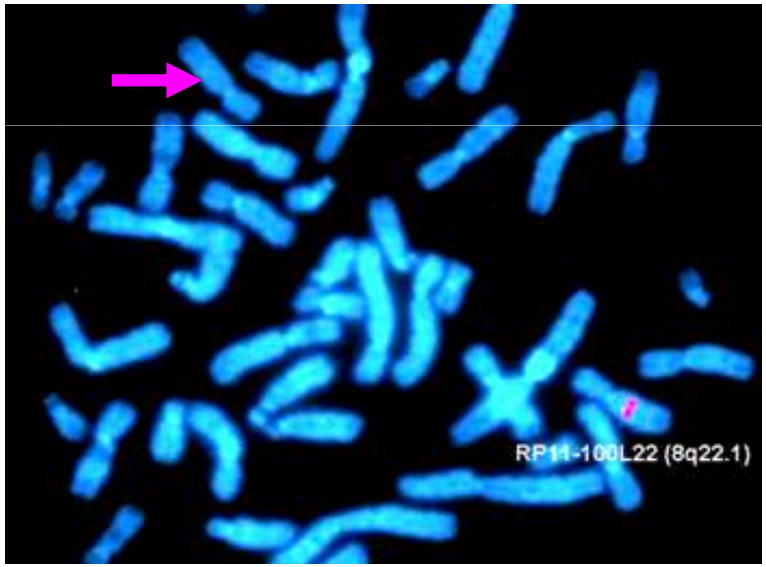
dup Xq12q13

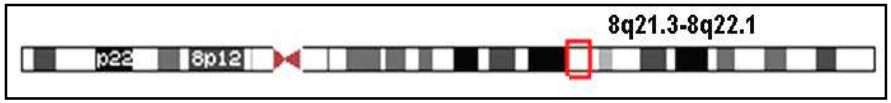
Bedeschi MF, Novelli A, Bernardini L, Parazzini C, Bianchi V, Torres B, Natacci F, Giuffrida MG, Ficarazzi P, Dallapiccola B, Lalatta F: Association of syndromic mental retardation with an Xq12q13.1 duplication encompassing the oligophrenin 1 gene. Am J Med Genet A. 146A:1718-24, 2008.

Nablus-mask like face syndrome (OMIM 608156)





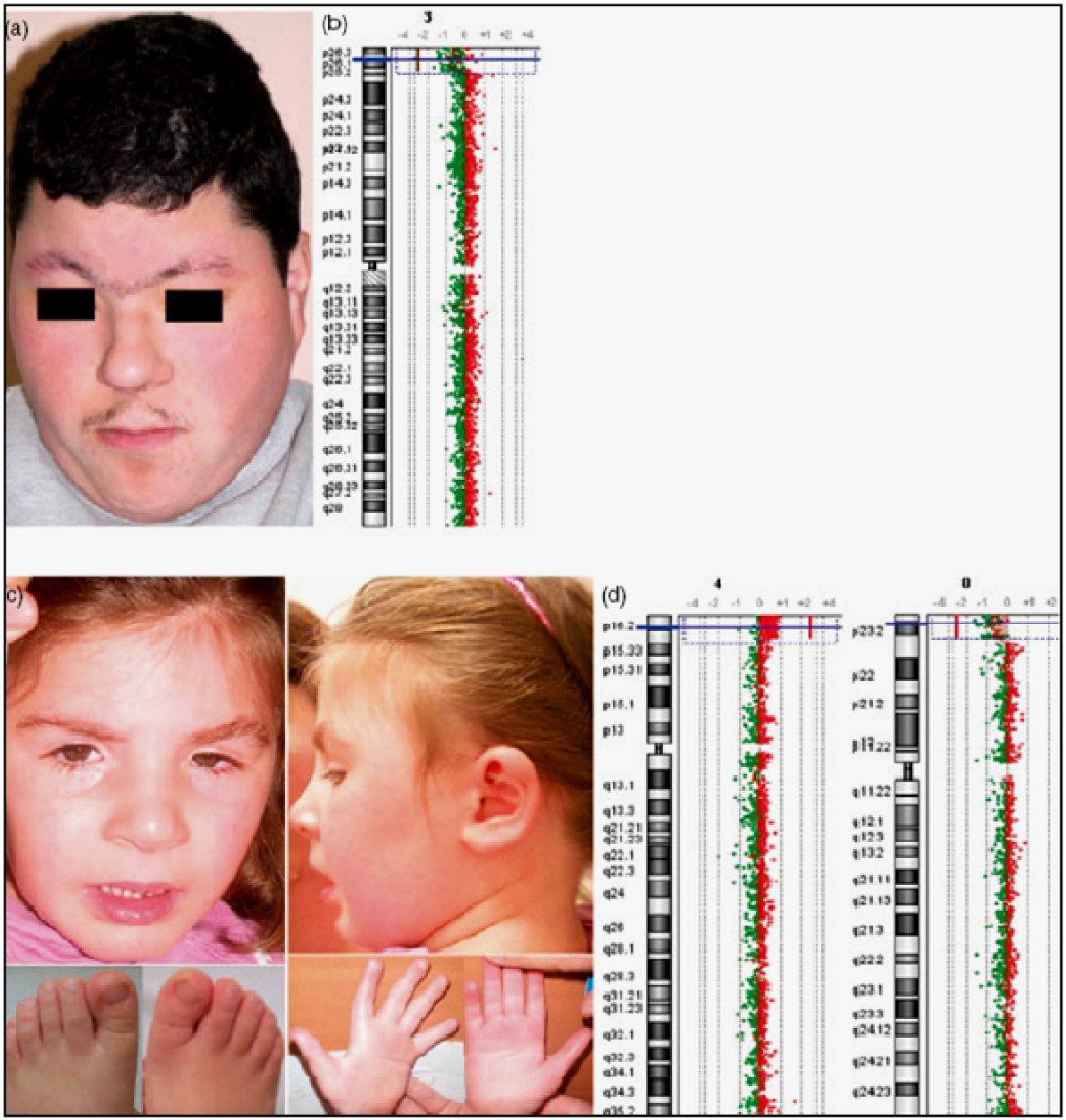




Salpietro CM, Briuglia S, Rigoli L., Merlino MV, Dallapiccola B: Confirmation of Nablus mask-like facial syndrome. Am J Med Genet, 121A, 283-285, 2003.

Shieh JTC, Aradhya S, Manning MA, Cherry AM, Brumblay J, Seaver LH, Salpietro CD, Bernardini L, Novelli A, Dallapiccola B, Hoyme HE: Nablus mask-like facial syndrome is caused by a microdeletion of 8q detected by array-based comparative genomic hybridization. Am J Med Genet, 140A: 1267-1273, 2006.

Sindrome di Young-Simpson: blefarofimosi, ritardo mentale, ipotiroidismo (OMIM 603736)

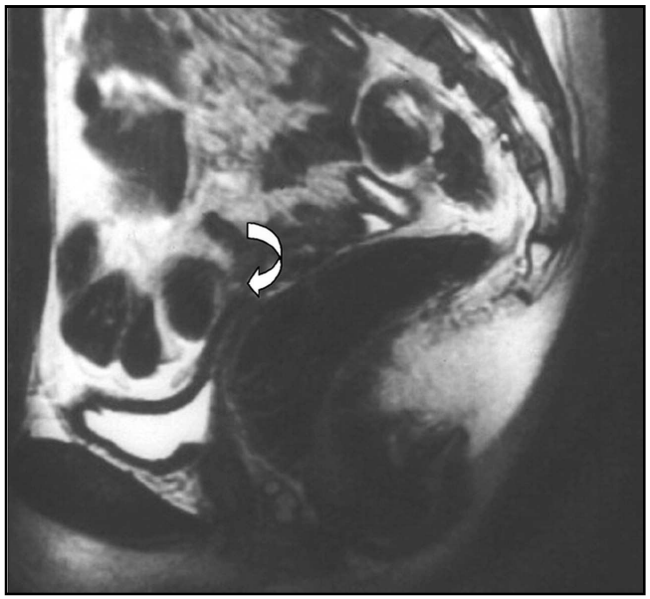


del 3p26.3-p25.5

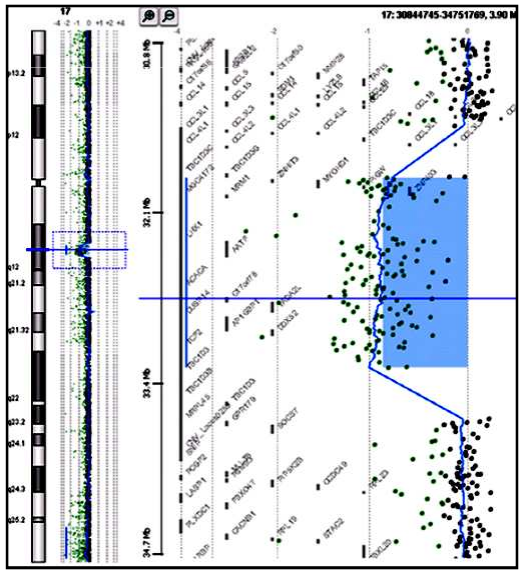
dup 4p16.3p16.1 del 8p23.3p23.1

Brancati F, Bernardini L, Cavalcanti DP, Romano C, Novelli A, Dallapiccola B: Genome rearrangements in patients with blepharophimosis, mental retardation and hypothyroidism, so-called Young-Simpson syndrome. Clin Genet 76:210-3, 2009.

La del17q12 causa un sottotipo della sindrome di Mayer-Rokitansky-Kuster-Hauser (OMIM 27700)







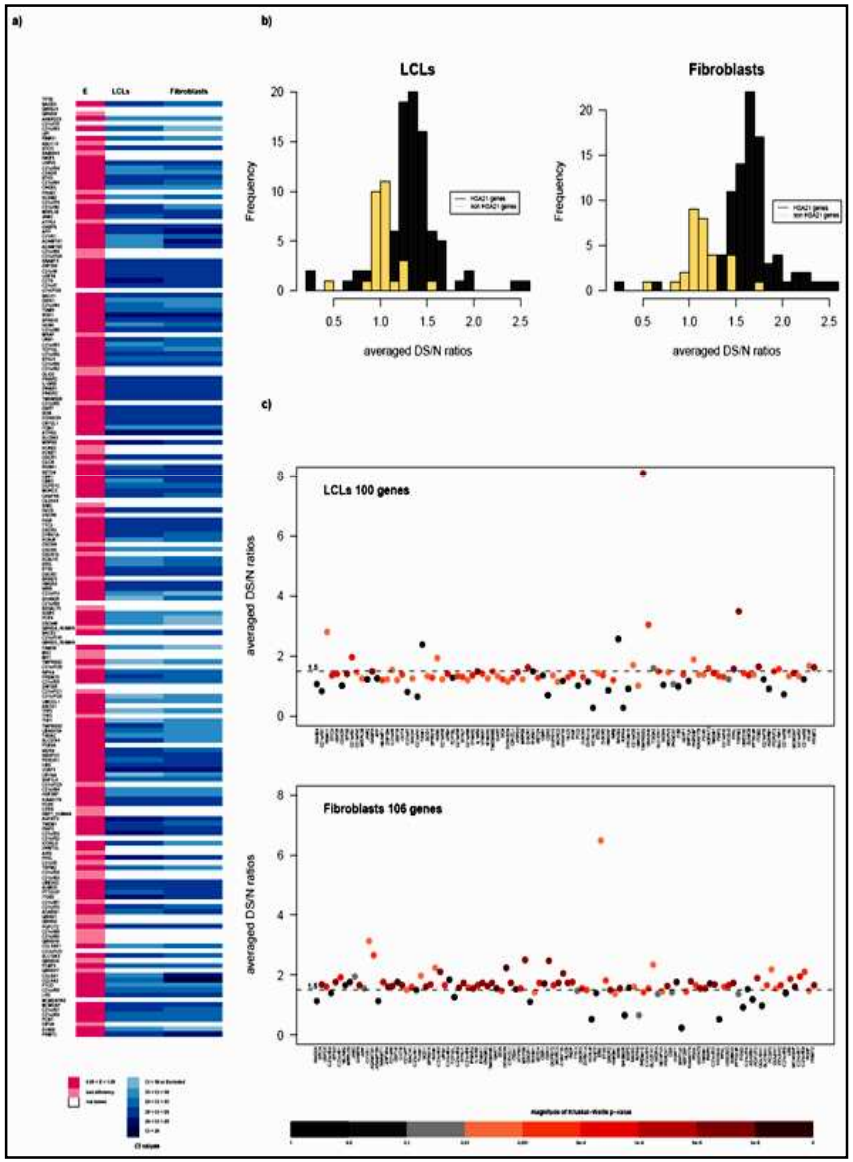
Bernardini L, Gimelli S, Gervasini C, Carella M, Baban A, Frontino G, Barbano G, Divizia MT, Fedele L, Novelli A, Béna F, Lalatta F, Miozzo M, Dallapiccola B: Recurrent microdeletion 17q12 as a cause of Mayer-Rokitansky-Huster-Hauser (MRKH) syndrome: two case reports. Orphanet J Rare Dis. 4:25, 2009.

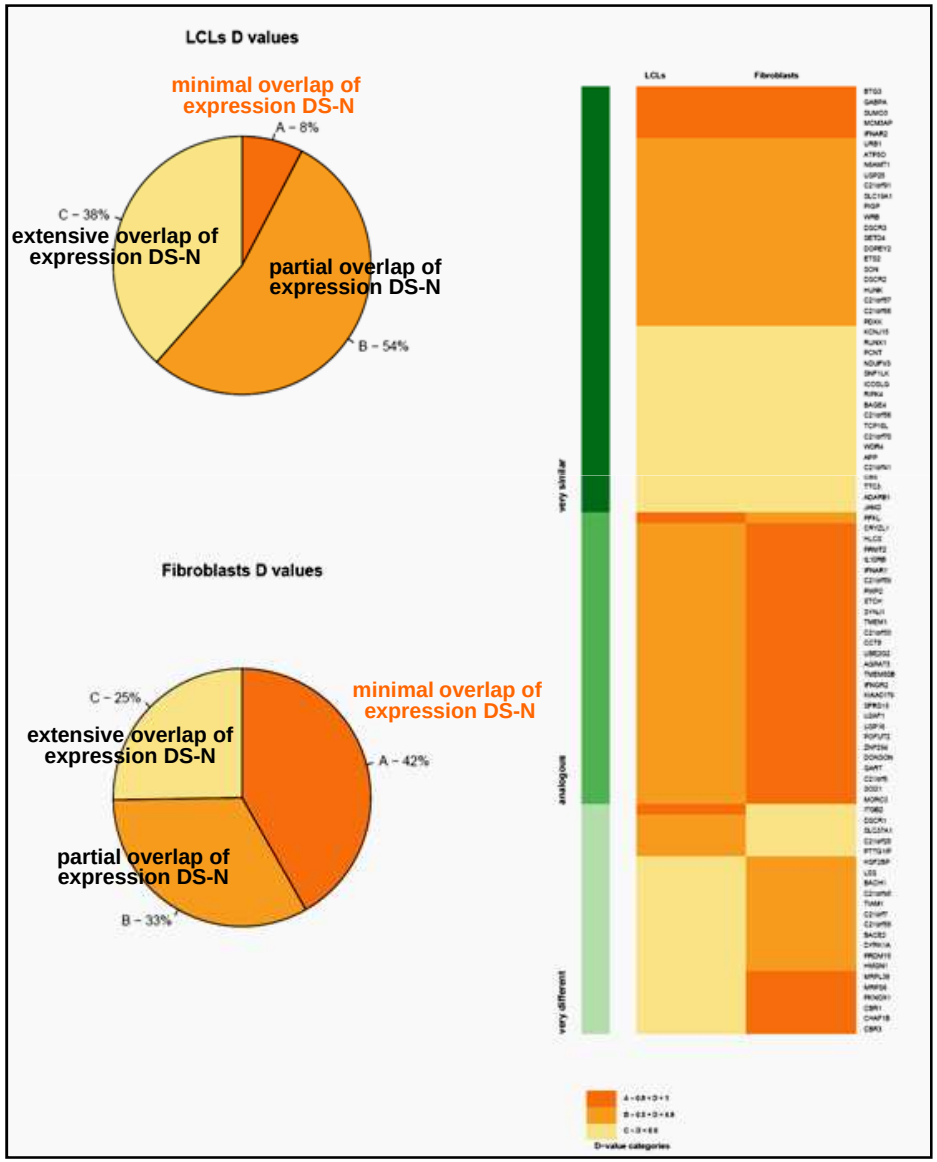


Natural Gene-Expression Variation in Down Syndrome Modulates the Outcome of Gene-Dosage Imbalance

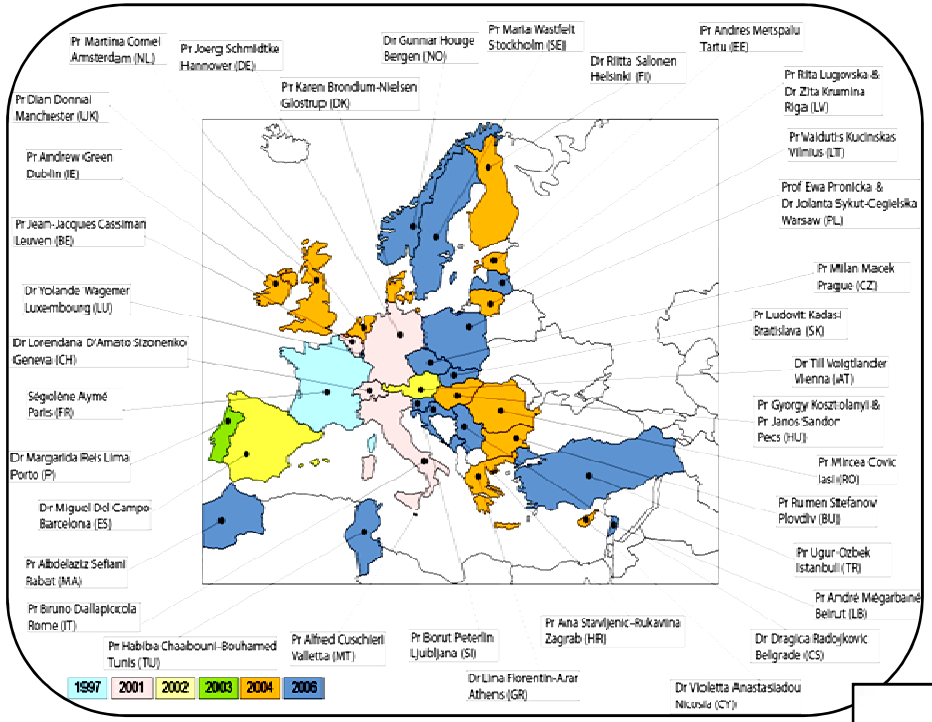
Paola Prandini, Samuel Deutsch, Robert Lyle, Maryline Gagnebin, Celine Delucinge Vivier, Mauro Delorenzi, Corinne Gehrig, Patrick Descombes, Stephanie Sherman, Franca Dagna Bricarelli, Chiara Baldo, Antonio Novelli, Bruno Dallapiccola, and Stylianos E. Antonarakis

The American Journal of Human Genetics Volume 81 August 2007





Sviluppo del database Orphanet dedicato alle malattie rare



Orphanet-Italia

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N. test diagnostici	3.245
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N. progetti di ricerca	615
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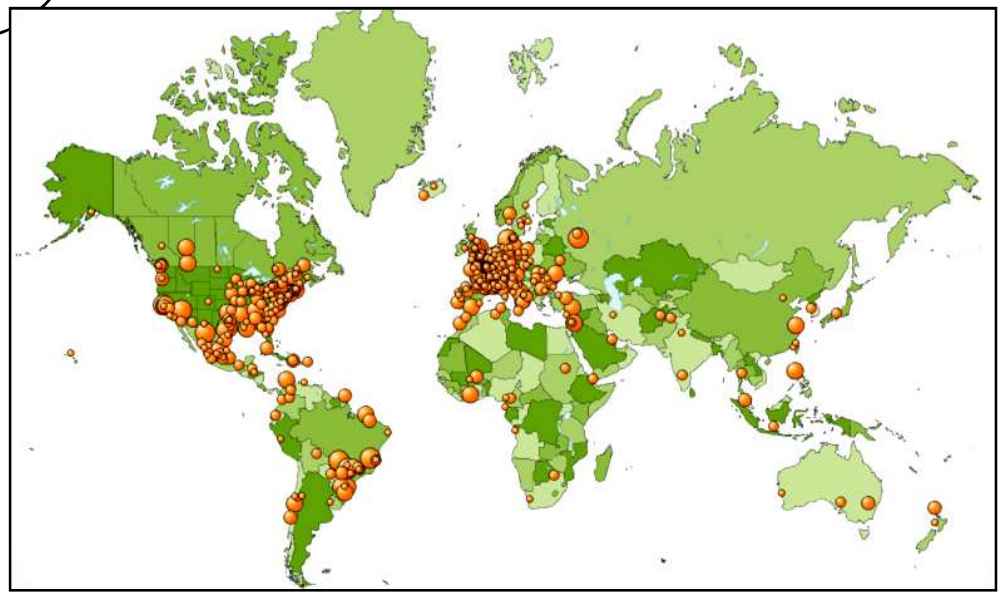
N. associazioni di pazienti	228

30 novembre 2009











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	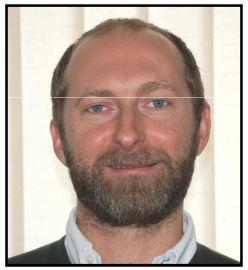	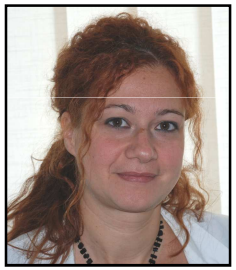				
Emanuele Bellacchio	Alessandro De Luca	Laura Bernardini	Sabrina Prudente	Enza Maria Valente	Rita Mingarelli	Francesco Brancati

> 5.500 diagnosi genetiche/anno
> 500 consulenze genetiche di 2° livello/anno
> 400 punti di *Impact Factor*/2009
> 450 pubblicazioni scientifiche internazionali 2000-2009