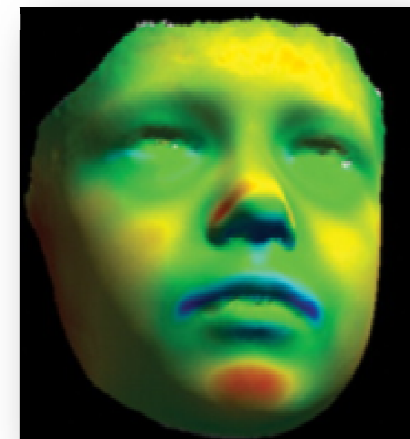


## La delezione 22q11.2 come prototipo di presa in carico multidisciplinare

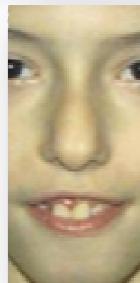
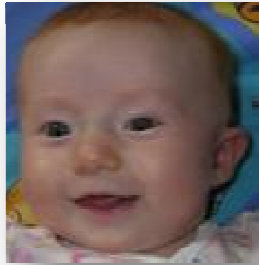
Bruno Dallapiccola



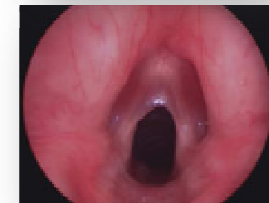
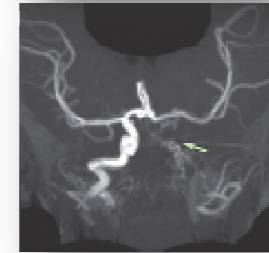
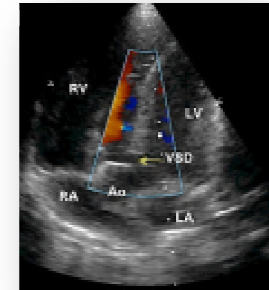


# Sindrome

*"Insieme di segni e sintomi che caratterizzano una particolare condizione clinica presente in una persona".*



- |   |      |
|---|------|
| • Cranio-facies/cavo orale                    | (16) |
| • Occhi                                       | (15) |
| • Orecchie/apparato uditivo                   | (10) |
| • Naso  | (5)  |
| • Cuore                                       | (15) |
| • Apparato vascolare                          | (9)  |
| • Cervello/sistema nervoso                    | (11) |
| • Faringe/laringe/vie aeree                   | (10) |
| • Reni/apparato gastrointestinale             | (13) |
| • Linguaggio                                  | (7)  |
| • Sviluppo cognitivo                          | (6)  |
| • Patologia psichiatrica/problemi psicologici | (16) |
| • Sistema immunitario                         | (5)  |
| • Apparato genitourinario                     | (3)  |
| • Apparato endocrino                          | (7)  |
| • Apparato muscolo-scheletrico                | (17) |
| • Cute  | (2)  |
| • Sequenze/associazioni                       | (5)  |
| • Arti  | (9)  |
| • Altro                                       | (4)  |

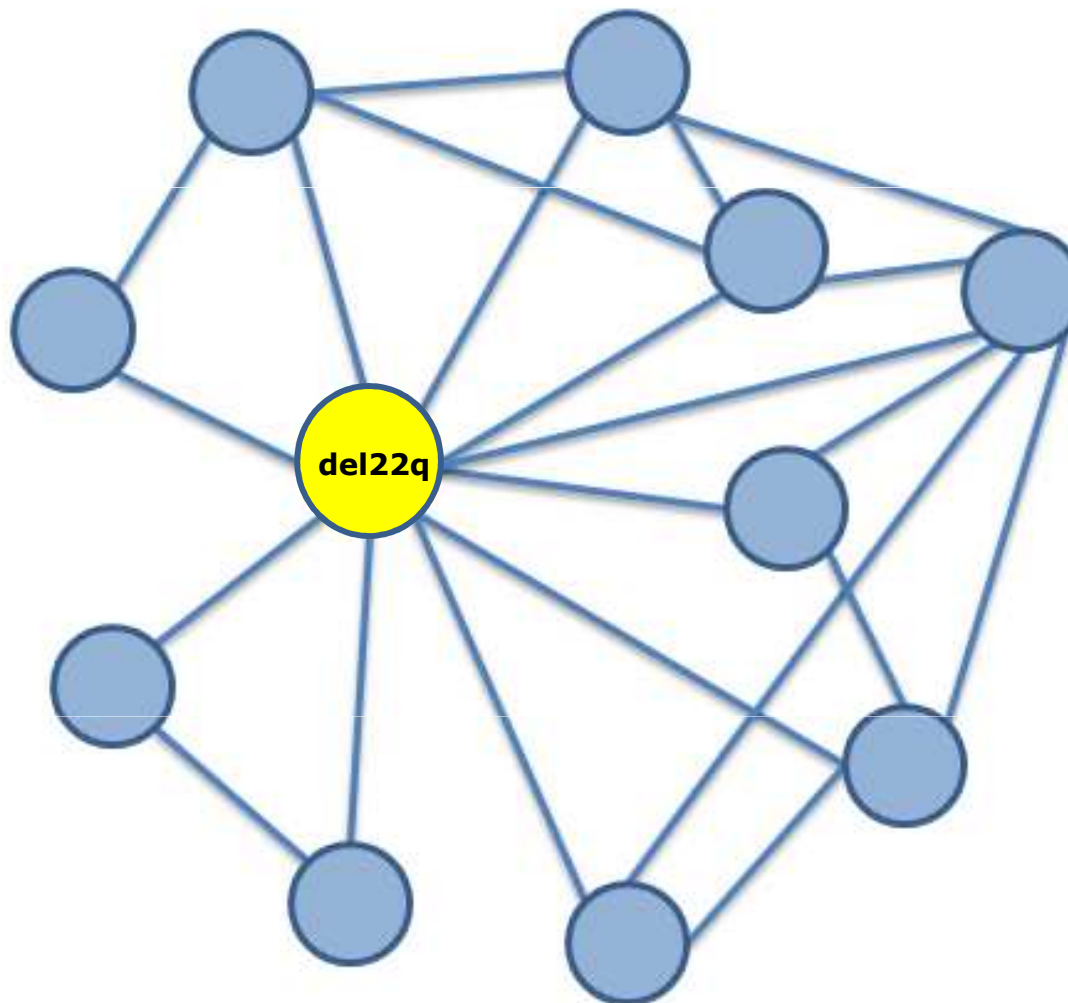




## Malattia multisistemica



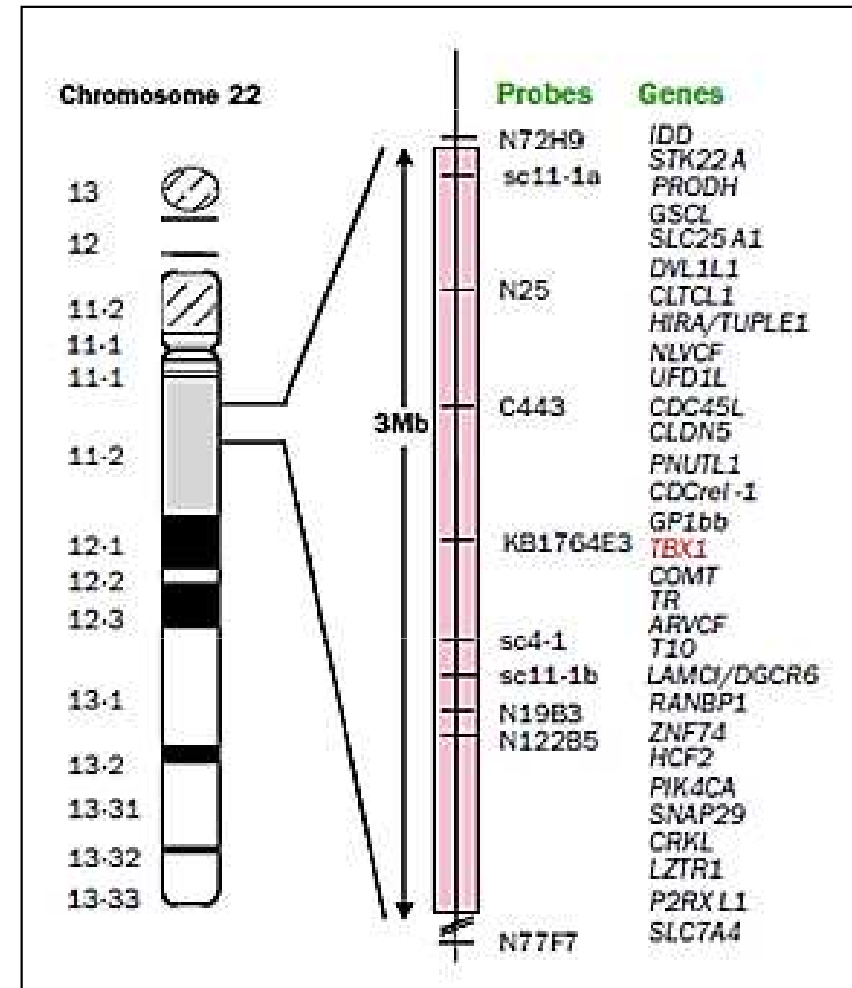
*"Malattia che colpisce diversi organi o tessuti o addirittura l'intero organismo".*





## Sindrome da "geni contigui"

"Condizione causata dallo sbilanciamento (delezione o duplicazione) di due o più geni fisicamente vicini sullo stesso cromosoma".

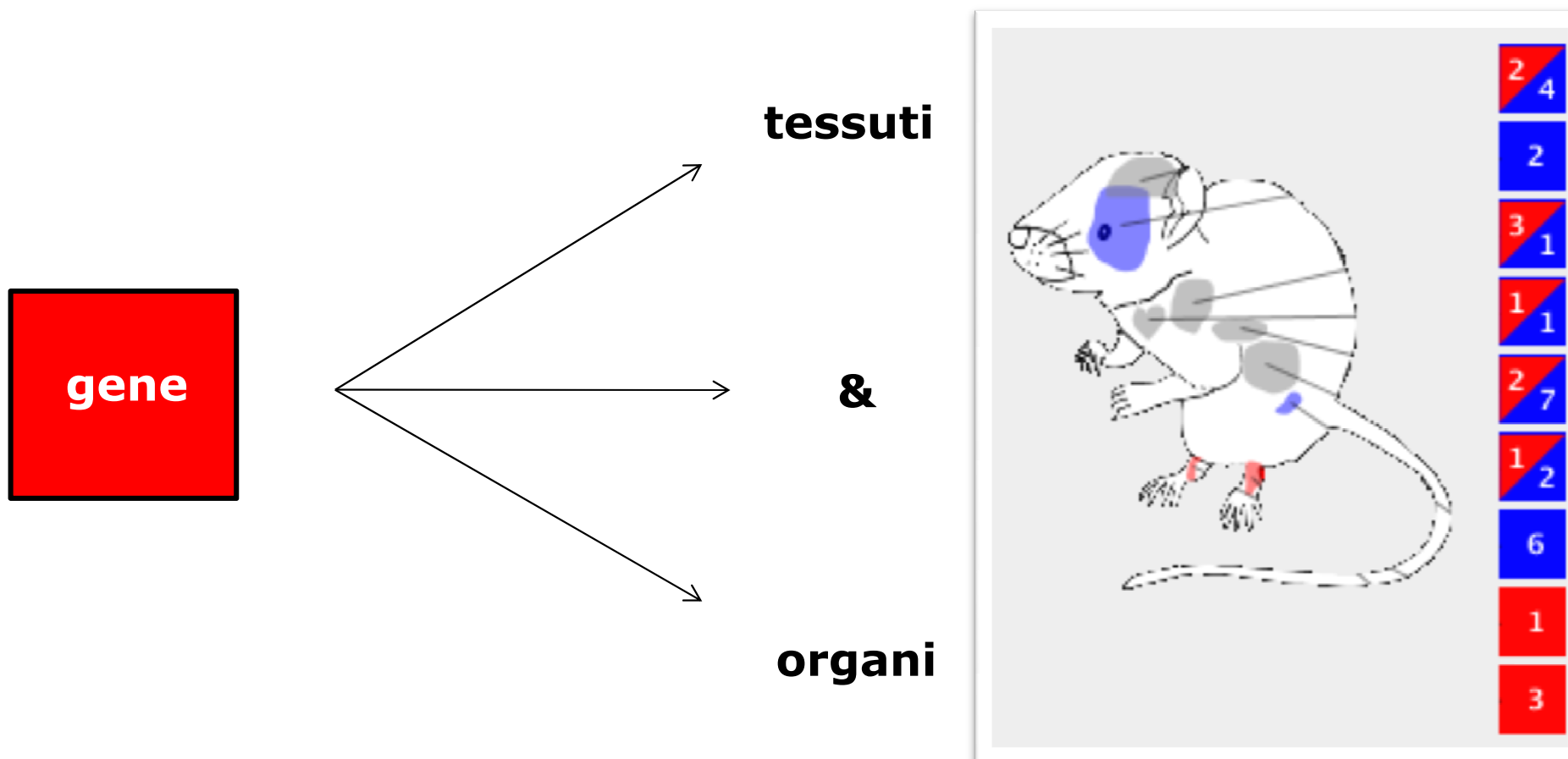




# Pleiotropismo



*"Un gene in grado di influenzare aspetti diversi del fenotipo di un essere vivente".*



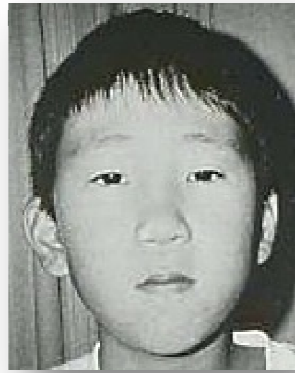




# Accorpamento di sindromi diverse nella delezione 22q11.2



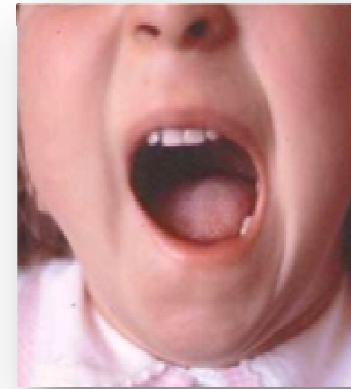
Sindrome di DiGeorge  
OMIM188400  
DiGeorge, 1968  
De la Chapelle et al,  
1981



*Conotruncal Anomaly  
Face Syndrome*  
OMIM 188400  
Takao et al., 1980  
Burn et al., 1993



Sindrome Velo-Cardio-  
Facciale – OMIM 192430  
Shprintzen et al., 1981  
Scambler et al., 1992

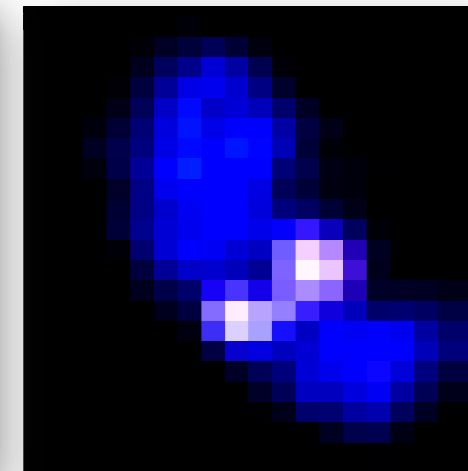
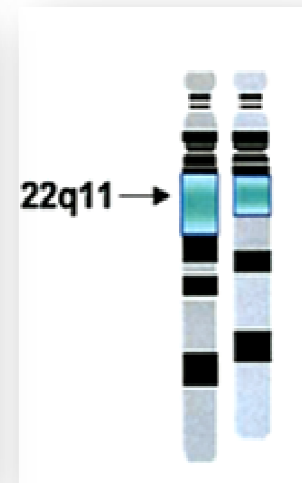
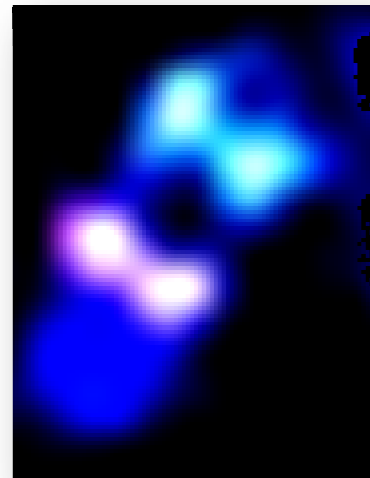
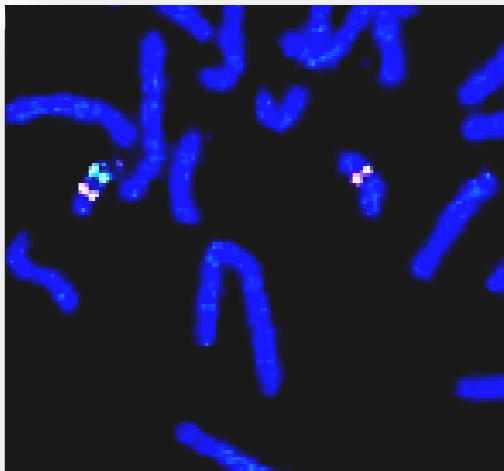


Sindrome di Cayler  
OMIM125520  
Cayler 1967  
Giannotti et al, 1994



Sindrome di Opitz GBBB  
OMIM 145410  
Opitz, 1987  
Zackai et al., 1996

...Sindrome di Takao, Sindrome di Sedlackova, Sindrome del III e IV arco branchiale, Sindrome di Shprintzen, Sindrome CATCH22...





## "Major gene"

"Un gene necessario e sufficiente da solo a causare una determinata condizione".

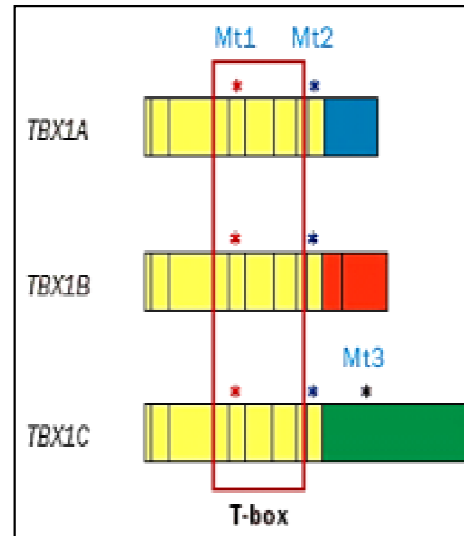
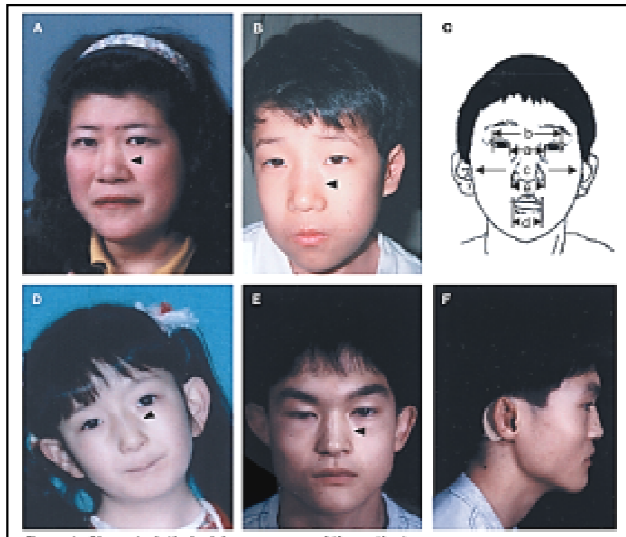
MECHANISMS OF DISEASE

**Mechanisms of disease**

Lancet 2003; 362: 1366-73

**Role of *TBX1* in human del22q11.2 syndrome**

Hisato Yagi, Yoshituki Furutani, Hiromichi Hamada, Takashi Sasaki, Shuichi Asakawa, Shinsei Minoshima, Fukiko Ichida, Kunitaka Joo, Misa Kimura, Shin-ichiro Imamura, Naoyuki Kamatani, Kazuo Momma, Atsuyoshi Takao, Makoto Nakazawa, Nobuyoshi Shimizu, Rumiko Matsuoka

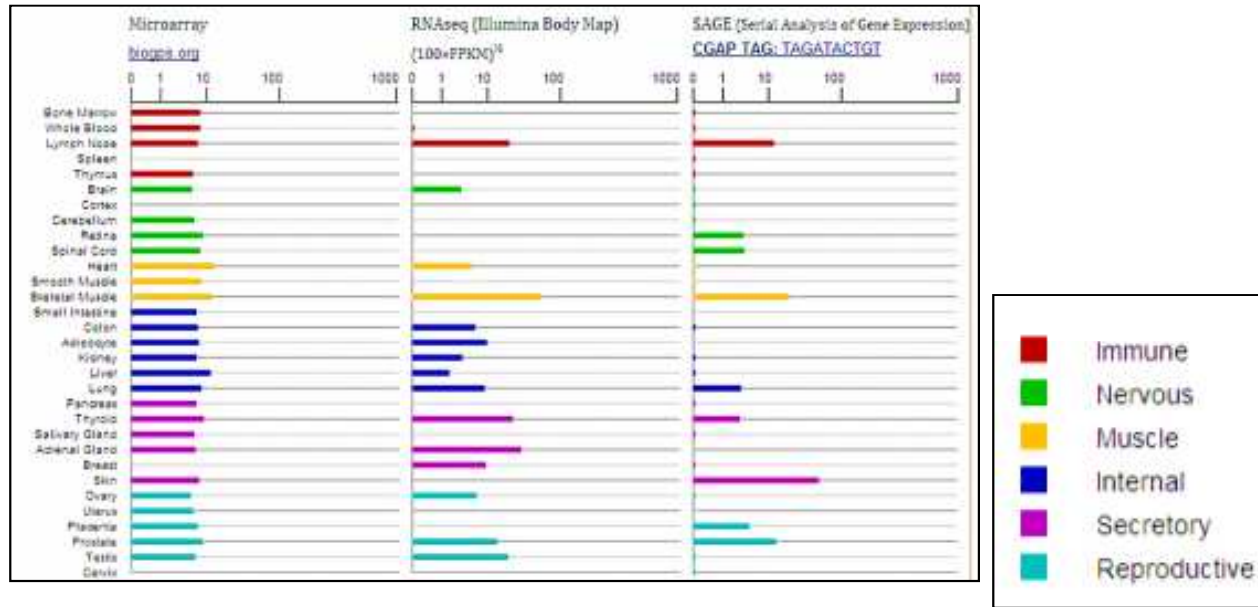


- 235 pazienti DGS/VCFS
- 225 con del 22q11.2
- 2 casi sporadici e 1 familiare con mutazioni in *TBX1*
- CONCLUSIONI: *TBX1* è un gene principale nel determinismo della sindrome da delezione 22q11.2

"*TBX1* è un fattore di trascrizione, appartenente alla famiglia dei geni «T-box», che svolgono ruoli importanti nella formazione dei tessuti e degli organi durante l'embriogenesi".



# Pleiotropismo del gene *Tbx1* e ruolo nello sviluppo degli archi brachiali



Dev. Biol. 288, 478-485, February 21, 2005, Copyright © 2005 by Cell Press

***TBX1* Is Responsible for Cardiovascular Defects in Velo-Cardio-Facial/DiGeorge Syndrome**

Bianca Merscher,<sup>1,2</sup> Birgit Purke,<sup>1,2</sup> Jonathan A. Epstein,<sup>1,2</sup> Joong Hyeon,<sup>1</sup> Anne Pasch,<sup>2</sup> Min Min Lu,<sup>2</sup> Raminik J. Xavier,<sup>2</sup>

***Tbx1* haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice**

Elizabeth A. Lindsay<sup>1</sup>, Francesca Vitelli<sup>2</sup>, Hong Su<sup>1</sup>, Masae Morishima<sup>1</sup>, Taehyung Hyun<sup>1</sup>, Tiziano Pramparo<sup>1</sup>, Vesna Jurcic<sup>1</sup>, George Ogunrinu<sup>1</sup>, Helen F. Sutherland<sup>1</sup>, Peter J. Scambler<sup>1</sup>, Allan Bradley<sup>1,2</sup> & Antonio Bahinski<sup>1</sup>

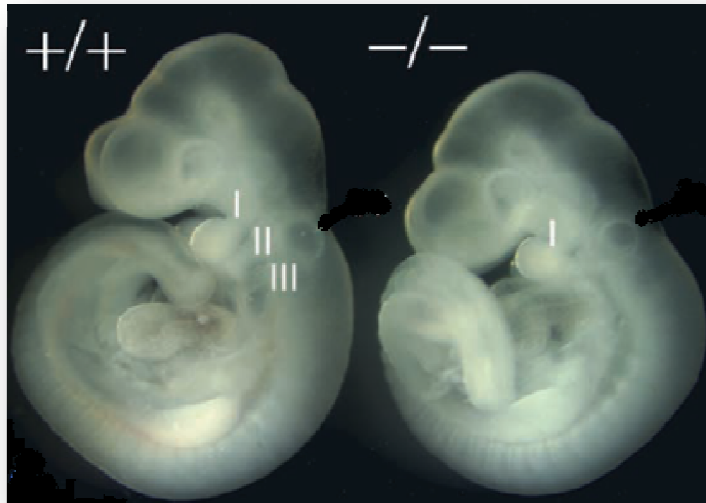
© 2001 Nature Publishing Group <http://genetics.nature.com>

article

nature genetics • volume 27 • march 2001

**DiGeorge syndrome phenotype in mice mutant for the T-box gene, *Tbx1***

Leslie A. Jerome & Virginia E. Papaioannou



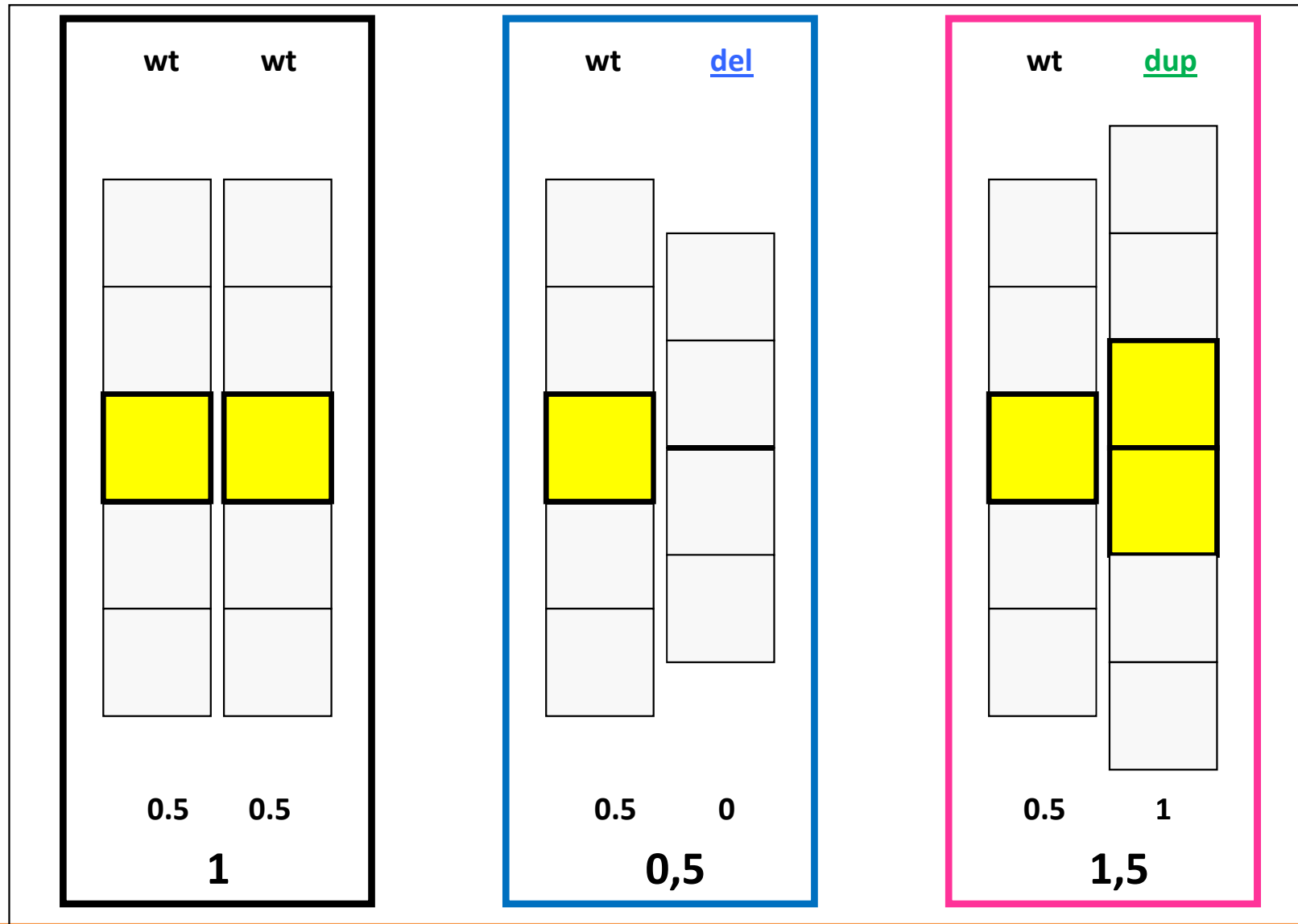
Jerome & Papaioannou, 2001



## Dose genica ed effetto di dose



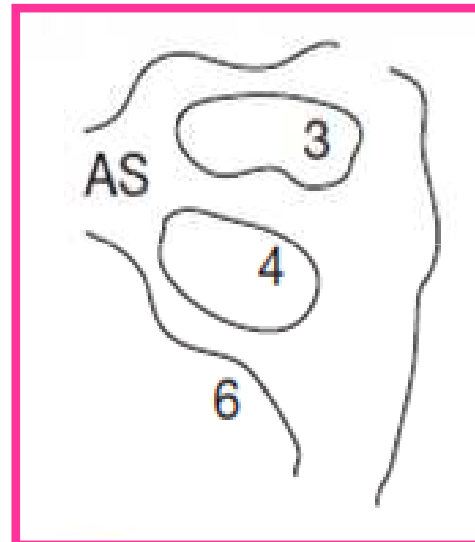
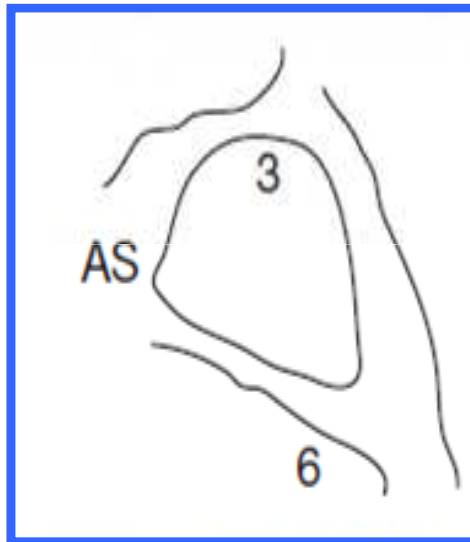
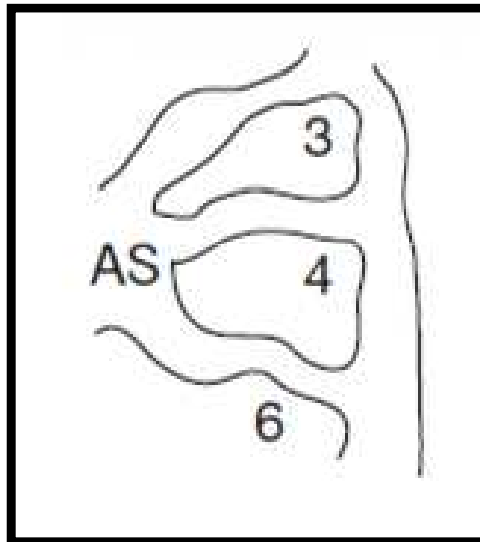
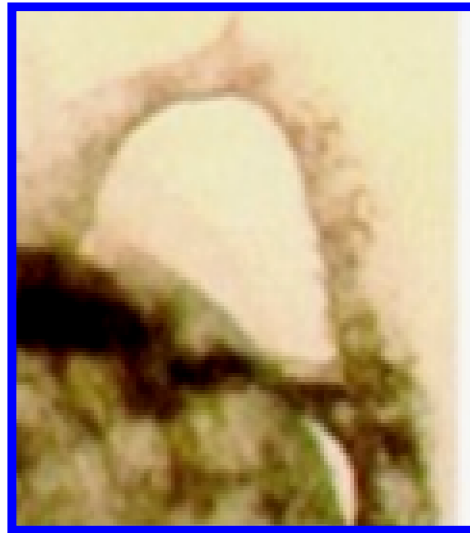
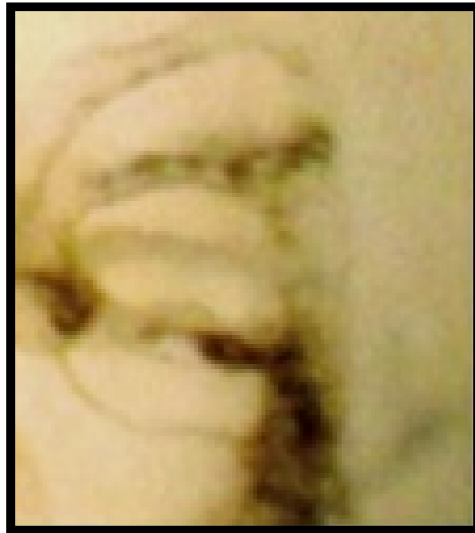
*"La dose genica è il numero di copie di un gene nella cellula o nel suo nucleo. Ogni cambiamento della dose genica può esitare in una modificazione del prodotto del gene".*







# Effetto primitivo di dose del gene *Tbx1* sullo sviluppo degli archi branchiali



***tbx1/tbx1***

***del**tbx1**/del**tbx1*****

***del**tbx1**/dup**tbx1*****

Lindsay et al., 2001



# Compenso della dose genica nei soggetti eterozigoti composti per delezione e duplicazione 22q11.2



*The NEW ENGLAND JOURNAL of MEDICINE*  
N ENGL J MED 360:12 NEJM.ORG MARCH 19, 2009

**BRIEF REPORT**

## Genetic Compensation in a Human Genomic Disorder

Nadège Carelle-Calmels, Pharm.D., Ph.D.,  
Pascale Saugier-Weber, Pharm.D., Ph.D., Françoise Girard-Lemaire, M.D.,  
Gabrielle Rudolf, Ph.D., Bérénice Doray, M.D., Eric Guérin, Pharm.D., Ph.D.,  
Pierre Kuhn, M.D., Mathilde Arrivé, B.S., Catherine Gilch, B.S.,  
Evelyne Schmitt, B.S., Séverine Fehrenbach, B.S., Albert Schnebelen, M.D.,  
Thierry Frébourg, M.D., Ph.D., and Elisabeth Flori, M.D.

**RESEARCH ARTICLE**

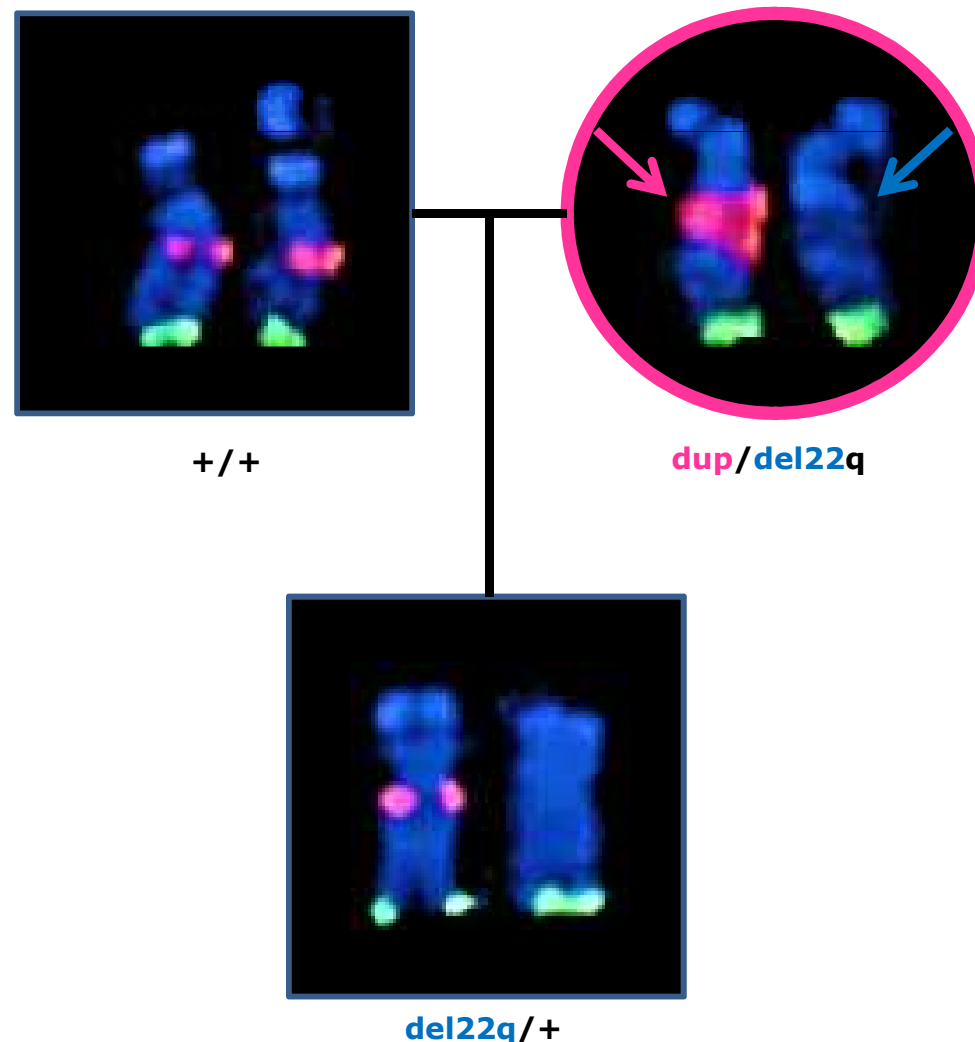
AMERICAN JOURNAL OF **medical genetics** PART A

## Genetic Dosage Compensation in a Family with Velo-Cardio-Facial/DiGeorge/22q11.2 Deletion Syndrome

Avishai A. Alkalay,<sup>1</sup> Tingwei Guo,<sup>2</sup> Cristina Montagna,<sup>2</sup> M. Cristina Digilio,<sup>3</sup> Bruno Dallapiccola,<sup>3</sup> Bruno Marino,<sup>4</sup> and Bernice Morrow<sup>2\*</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York  
<sup>2</sup>Department of Genetics, Albert Einstein College of Medicine, Bronx, New York  
<sup>3</sup>Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy  
<sup>4</sup>University La Sapienza, Pediatric Cardiology, Rome, Italy

Volume 155, Issue 3, pages 548-554, March 2011

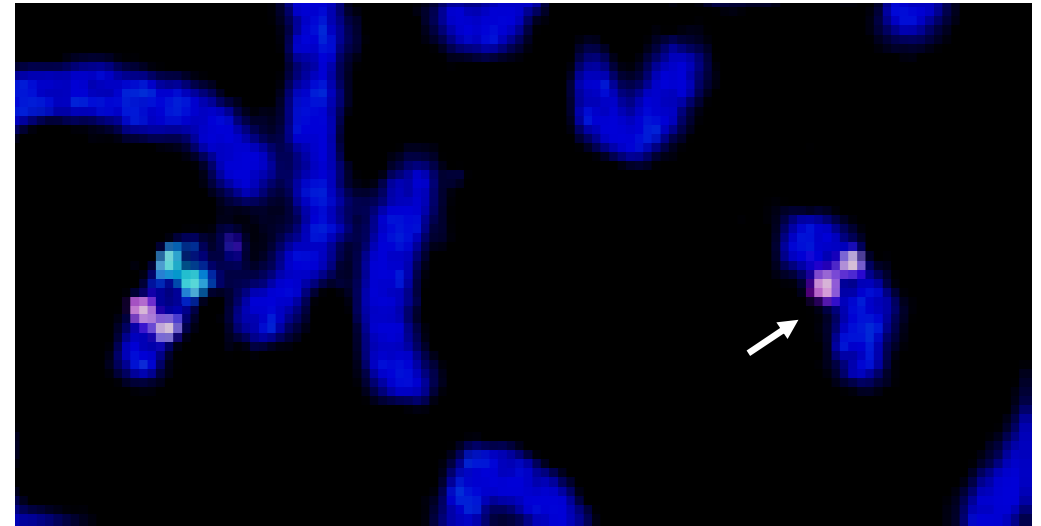




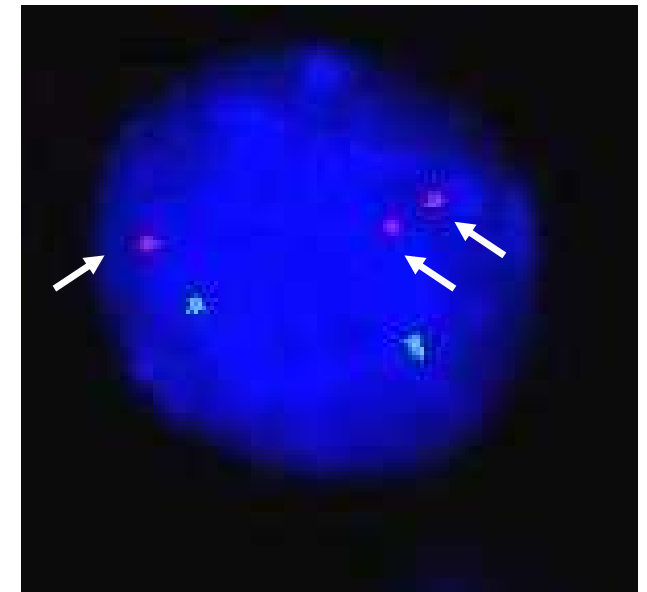
# "Tipo" e "controtipo" della regione 22q11.2



del 22q11.2  
sindrome  
velo-cardio-facciale



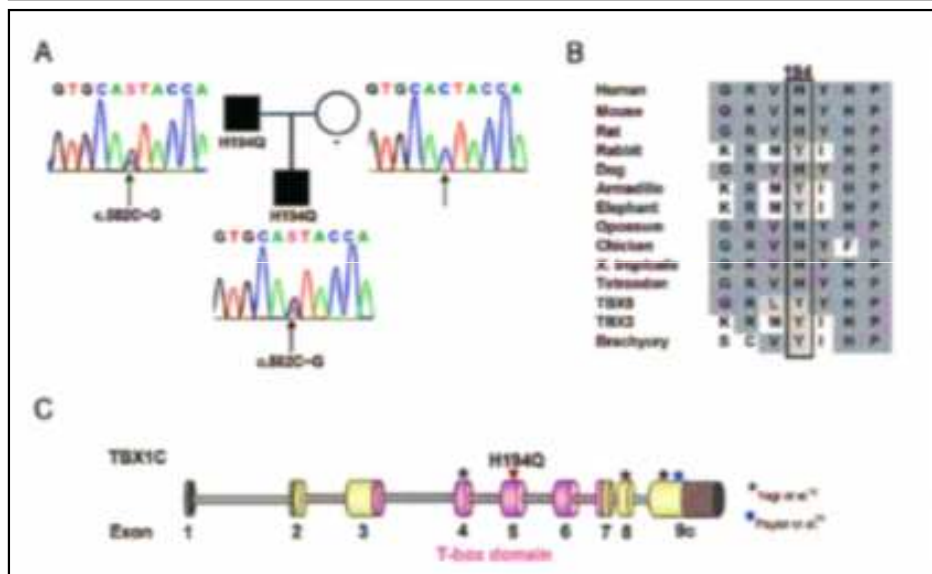
dup 22q11.2





# Human *TBX1* Missense Mutations Cause Gain of Function Resulting in the Same Phenotype as 22q11.2 Deletions

Christiane Zweier, Heinrich Sticht, Inci Aydin-Yaylagül, Christine E. Campbell, and Anita Rauch



guadagno di funzione

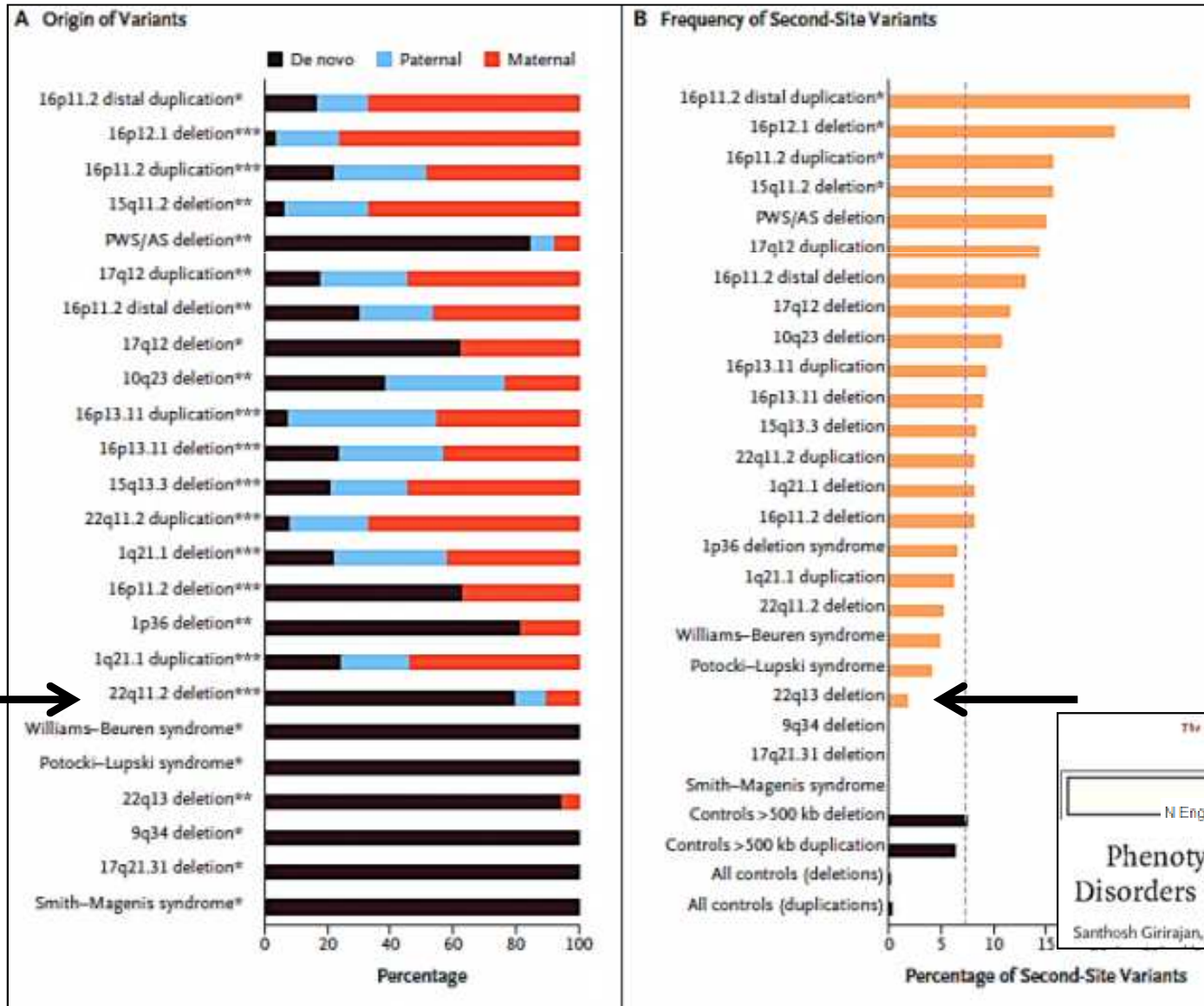
Table 1. Overview of Phenotype in 22q11.2 Copy-Number Aberrations and *TBX1* Mutations

Trait	<i>TBX1</i> Stop Mutation <sup>12,14</sup> (n = 7)	F148Y <sup>12</sup> (n = 1)	G310S <sup>12</sup> (n = 1)	H194Q (n = 2)		Deletion <sup>2</sup> (n = 558) (%)	Duplication <sup>27</sup> (n = 35) <sup>a</sup> (%)	
				Patient	Father			
Congenital heart defect	3	+	+	-	-	57	19	●
Hypocalcemia	1	-	+	-	-	60	...	
Cleft palate	-	-	-	-	-	9	33	●
Velopharyngeal insufficiency	3	+	+	-	-	32	59	●
Short stature	-	-	-	+	+	36	50	●
Mental retardation and/or developmental delay	-	-	-	(+)	-	38	91	●
Psychiatric disorders	2	-	-	-	-	30 <sup>29</sup>	...	
VCFS facial gestalt <sup>b</sup>	7	+	+	+	+	100 <sup>12</sup>	...	



# Malattia geneticamente complessa

*"La complessità è la caratteristica di quelle condizioni per le quali è spesso impossibile identificarne tutti i meccanismi".*

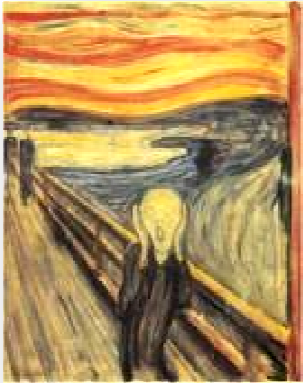




## Malattia evolutiva



"Condizione patologica il cui quadro clinico si modifica con il tempo".



RESEARCH ARTICLE

AMERICAN JOURNAL OF  
**medical genetics**  
Neuropsychiatric Genetics

PART  
**B**

### Schizophrenia Two-Hit Hypothesis in Velo-Cardio Facial Syndrome

Hywel J. Williams,<sup>1</sup> Stephen Monks,<sup>2</sup> Kieran C. Murphy,<sup>2</sup> George Kirov,<sup>1</sup> Michael C. O'Donovan,<sup>1</sup> and Michael J. Owen<sup>1\*</sup>

TABLE II. PLINK CNV Burden Analysis in Discovery VCFS Sample

Test	VCFS + Psychosis	VCFS – Psychosis	P-value
N	41	50	n/a
Rate	1.8	2.1	0.77
Total kb	875	533	0.09
Average kb	354	227	0.02

N, total number of CNVs; Rate, number of CNVs per individual; Total kb, total length (kb) of genome spanned by CNVs; Average kb, average size (kb) of each CNV.

P-value, empirical P-value from PLINK obtained after 10,000 permutations.

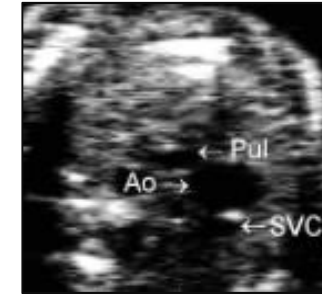


## Malattia cronica

*"Condizione patologica di lunga durata, tendenzialmente quanto la vita del soggetto".*



*espressione prenatale*



*congenita*

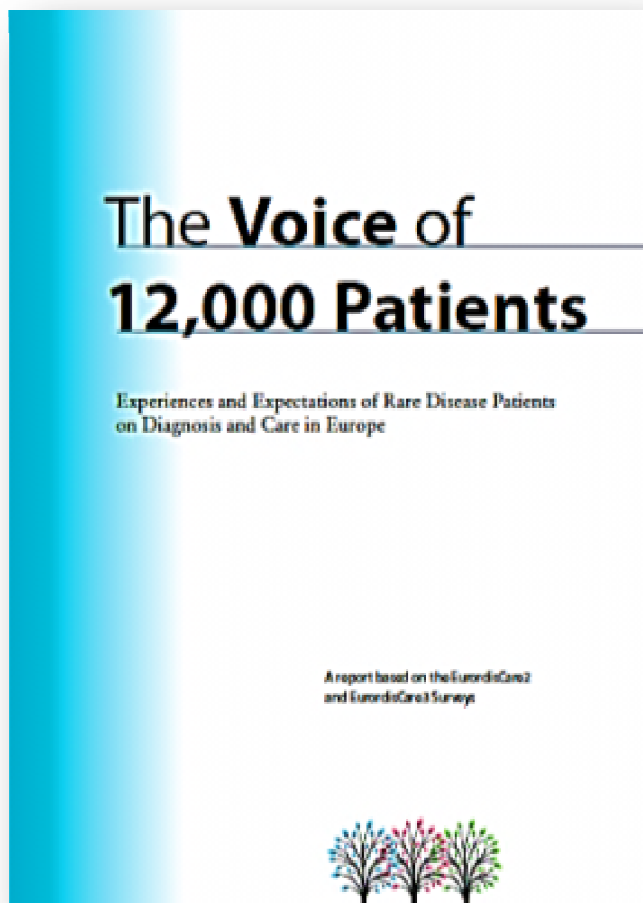


*diagnosticata nella vita adulta*





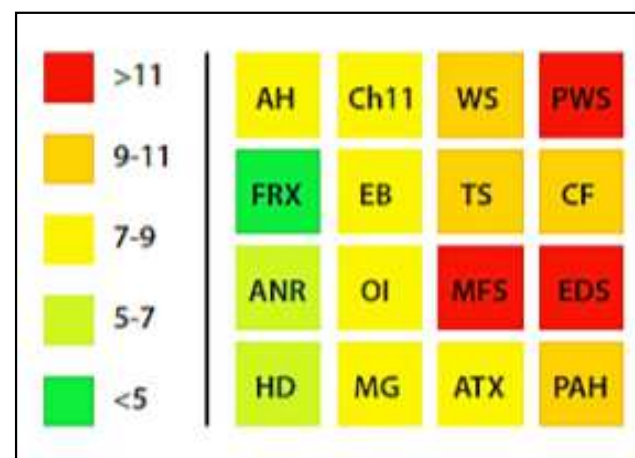
## Presa in carico multidisciplinare



### INDIVIDUAL NEEDS

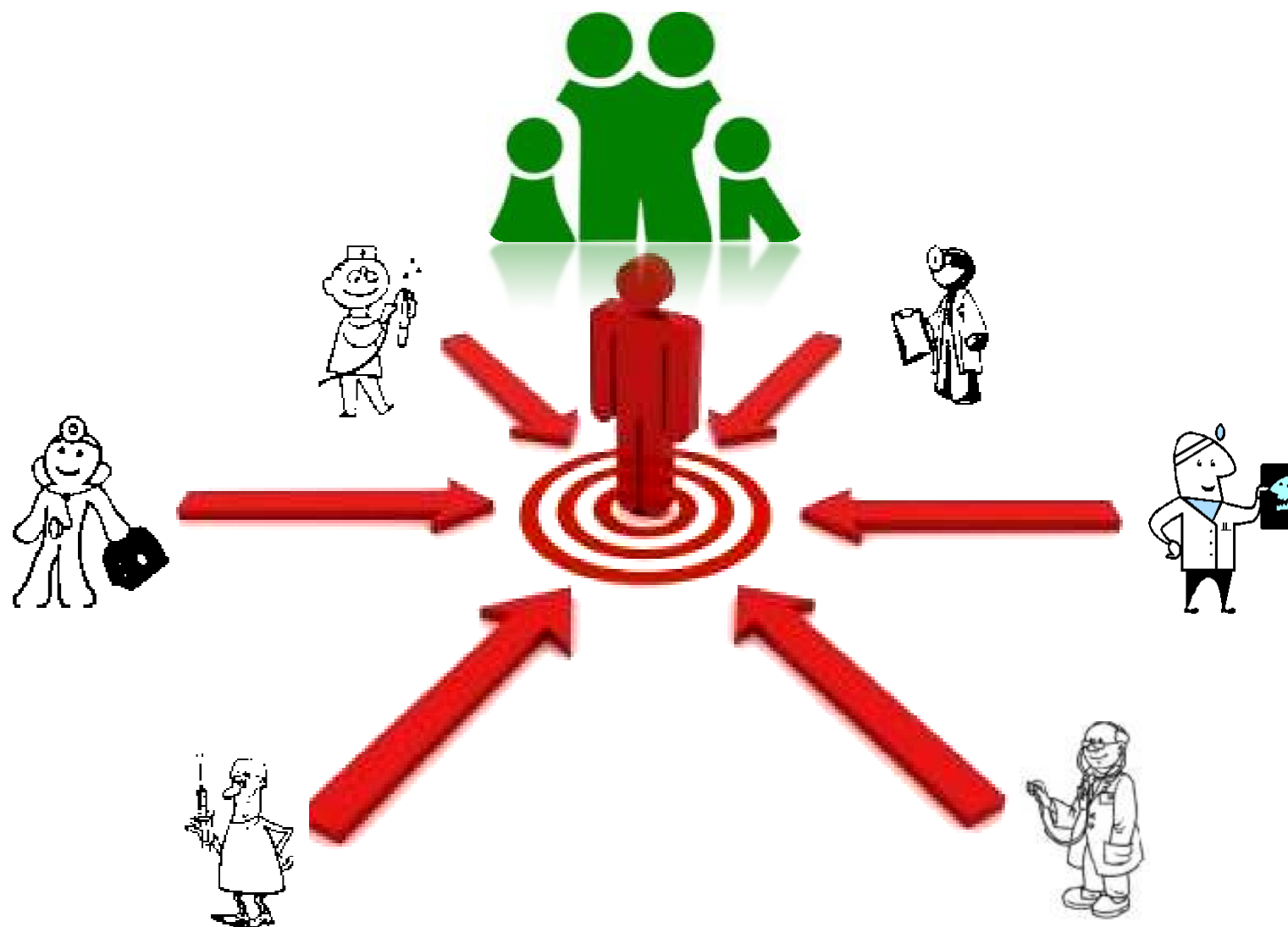
Considering the overall population of respondents, the average individual needs of respondents included 9.4 different medical services. More specifically, these included four kinds of consultations, three types of medical exams and 2.4 types of additional care services. What may seem to be a considerable number of medical services to the healthy observer is a reality for rare disease patients.

«Il numero medio di servizi medici richiesti è 9.4, compresi 4 tipi di consulenza, 3 esami medici e 2.4 altri servizi».





# Presa in carico multidisciplinare Il modello dell'Ospedale Bambino Gesù





*"Transition is the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-orientated health care systems"*

*Blum et al, 1993*

1 in 17 people will develop a rare disease at some point in their lives



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- About Rare Diseases
- Living with a Rare Disease
- A UK Rare Disease Strategy
- Rare Disease Day
- Rare Disease Policy
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You are here: ➤ Home / ➤ Living with a rare disease / ➤ Experiences of Rare Diseases report / Overview

## Overview of Experiences of Rare Diseases: An Insight from Patients and Families

There are over 6,000 recognised rare diseases each with different symptoms and prognoses, yet our research highlights that patients and families frequently face common problems regardless of which rare condition they are living with.

Some of the common problems experienced included:

- Difficulties in securing a correct diagnosis, with patients often reporting severe delays in diagnosis and multiple misdiagnoses.
- Patients and families struggling to access information on their condition and experiencing a lack of support with both their medical and non-medical needs.
- Patients reporting that their care is badly coordinated, particularly around the time of transition from paediatric to adult services.
- Patients having difficulties in accessing all the services they require for their condition.





## Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

Anne S. Bassett, MD,\* Donna M. McDonald-McGinn, MS, CGC,\* Koen Dewriendt, MD, Maria Cristina Digilio, MD, Paula Goldenberg, MD, MSW, Alex Habel, MD, Bruno Marino, MD, Solveig Oskarsdottir, MD, PhD, Nicole Philip, MD, Kathleen Sullivan, MD, PhD, Ann Swillen, PhD, Jacob Vorstman, MD, PhD, and The International 22q11.2 Deletion Syndrome Consortium\*\*

*"Le linee-guida sono raccomandazioni di comportamento clinico, prodotte attraverso un processo sistematico, con lo scopo di assistere i medici e i pazienti nelle decisioni sulle modalità di assistenza più appropriate, in specifiche circostanze cliniche".*

**Table II. Recommended assessments for 22q11.2 deletion syndrome\***

Assessment	At diagnosis	Infancy (0-12 months)	Preschool age (1-5 years)	School age (6-11 years)	Adolescence (12-18 years)	Adulthood (>18 years)
Ionized calcium, parathyroid hormone <sup>†</sup>	✓	✓	✓	✓	✓	✓
Thyrotropin (thyroid-stimulating hormone) <sup>†</sup>	✓	✓	✓	✓	✓	✓
Complete blood cell count and differential (annual)	✓	✓	✓	✓	✓	✓
Immunologic evaluation <sup>‡</sup>	✓	✓ <sup>§</sup>	✓ <sup>§</sup>			
Ophthalmology	✓	✓	✓			
Evaluate palate <sup>¶</sup>	✓	✓	✓			
Audiology	✓	✓	✓			✓
Cervical spine (>age 4 years)			✓ <sup>  </sup>			
Scoliosis examination	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
Electrocardiogram	✓					✓
Echocardiogram	✓					
Development <sup>**</sup>	✓	✓	✓			
School performance				✓	✓	
Socialization/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioral <sup>††</sup>	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counseling <sup>‡‡</sup>	✓				✓	✓
Gynecologic and contraceptive services					✓	✓

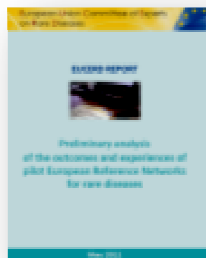


Centro Esperto



ambulatorio dedicato

European Reference Network (ERN)



territorio

il bambino  
diventa adulto

associazioni