

# MALATTIE RARE CONOSCKERLE PER RICONOSCKERLE

Castellaneta Marina (TA), 18-19 maggio 2012



associazione  
malattie  
metaboliche  
e genetiche  
puglia

O.N.L.U.S

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## La prevenzione: un piano regionale per la Puglia. Perché?

*Rita Fischetto*

*Referente Genetica Clinica*

*U.O.C. Malattie Metaboliche Diabetologia*

*A.O.U. Policlinico-Giovanni XXIII*

*Bari*



- CRESCITA CONOSCENZE delle basi biologiche
- organizzazione rete centro-periferia
- organizzazione famiglie
- ricerca clinica.

NCBI Online Mendelian Inheritance in Man (OMIM) Johns Hopkins University

Search PubMed for Kabuki syndrome

Enter one or more search terms.  
 Use Limits to restrict your search by search field, chromosome, and other criteria.  
 Use Index to browse terms found in OMIM records.  
 Use History to retrieve records from previous searches, or to combine searches.

NCBI is implementing changes to help you find current content in OMIM based on resources at NCBI, and then directing you to [omim.org](http://omim.org). Please be aware that you will leave NCBI to view OMIM records. Access to full records from NCBI (e.g. web, ftp, email) will no longer be supported.

### OMIM<sup>®</sup> - Online Mendelian Inheritance in Man<sup>®</sup>

Welcome to OMIM<sup>®</sup>, Online Mendelian Inheritance in Man<sup>®</sup>. OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

NLM's Profiles in Science -- The McKusick Papers [More...](#)

Orphanet Accesso al sito italiano di Orphanet

Italia

- > Homepage
- > Team/Contatti
- > Governance
- > Partner del progetto
- > Link utili
- > Registra la tua attività

**I servizi di Orphanet**

- Un elenco e una classificazione delle malattie rare
- Un'enciclopedia
- Una raccolta di informazioni: consulenze cliniche, laboratori di diagnosi, progetti di ricerca, registri, sperimentazioni cliniche, associazioni di pazienti
- Un elenco di farmaci orfani
- Linee guide, reports
- Una newsletter

Accedi a questi servizi in: Italiano OK

Benvenuti nella pagina web italiana di Orphanet

**In questo sito potrete trovare notizie, eventi e documenti sulle malattie rare e i farmaci orfani rilevanti a livello nazionale.**

Se invece cercate informazioni sulle malattie rare, sui farmaci orfani e sui servizi specialistici disponibili in Italia e anche negli altri paesi, potete visitare il sito web del database di Orphanet al seguente indirizzo: [www.orpha.net](http://www.orpha.net).

**L'ATTUALITA' IN ITALIA**

**SUL TAVOLO DEL MINISTERO DELL'ECONOMIA LE 109 MALATTIE RARE DA INSERIRE NEI LEA**

Nel nuovi LEA, sul tavolo del Ministero dell'Economia per l'approvazione, sono state inserite 109 nuove malattie rare che vanno ad aggiungersi alle 500 già codificate. Lo ha annunciato il ministro della Salute, Ferruccio Fazio, nel corso della conferenza stampa di presentazione di una



Archivio Med. di base - [ANAGRAM]

DE [DIPLOMA] [SISTEMI] [RECORD] [RIPETIZIONE]

N° CASTELLA: 520      URBAN N. Controllo: 1000

CODICE ROSSO:      NOME: GIOVANNI      Sesso:

Sesso:      Data di nascita: 28/02/2011      Città:      Codice Fiscale: 05569110764

Patente:      Matricola:

Indirizzo:      Città:      CAP:      Telefono:

Indirizzo Email:      Stato Civile:      DECLUSO

data 1° diagnosi:      DIAGNOSI:

ATTENZIONE:

Fenilchetonuria	196
S. Down	126
Neurofibromatosi	115
Aneuploidie altri cromosomi	64
S. Marfan	61
OA ; Apatie; Ciclo urea	58
Microarrangiamenti cromosomici	36
MPS	32
S. Turner	26
S. Martin Bell	23
S. Williams	19
S. De George VCF	12
S. Prader Willi	9
M. Gaucher	5

## Nel 2000 “Progetto Genoma Umano”

- Malattie Rare: lo studio di correlazione “genotipo-fenotipo” ;
- Malattie Complesse: l’identificazione di “loci genici” di suscettibilità (Diabete, Psoriasi) ;
- Nanotecnologie, terapia genica, medicina rigenerativa



ESPRESSIONE MENDELIANA DI MALATTIA: regolazione  
secondo le leggi mendeliane.

Reverse genetics

EZIOLOGIA COMPLESSA DEI FENOTIPI:

Interazione gene-ambiente

Energonomica

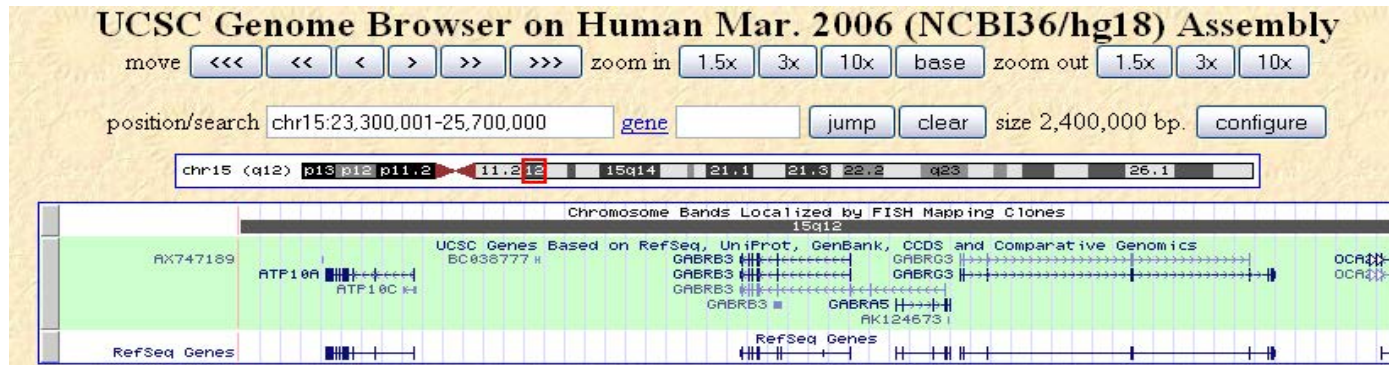
Epigenetica

Recombinogenomica

Effetti transgenerazionali

# ANALISI GENOMA

## CGH –Array: ibridazione genomica comparativa



**CNV/ CNP: variazioni/polimorfismi del numero di copie.**

Popolazione generale: 3-7 varianti genomiche  
(0,02% genoma totale)

WORK IN PROGRESS: - completamento lista varianti comuni

- definizione di varianti “fattori di suscettibilità”

# CGH- array

**Dati preliminari su un campione di popolazione selezionata (!) presso il ns. Centro di Riferimento per le Malattie Rare in età pediatrica.**

**Periodo: 2006- 2011.**

**Quesito clinico iniziale: ritardo cognitivo/ delle acquisizioni**

**- FILTRO CLINICO**

- con/ senza epilessia

- con/ senza dismorfismi cranio-facciali

- con/ senza alterazioni scheletriche e/o neuroradiologiche

**- FILTRO LABORATORISTICO**

**- ASSOCIAZIONI ANAMNESTICHE**

- familiarità

- con/senza patologia materna gravidica;

- con/senza patologia paterna/ materna pre-gravidica

# CGH-Array

N° pazienti selezionati: 91

N° pazienti positivi: 36

N° pazienti con diagnosi “de novo”: 27

N° pazienti con un genitore portatore: 6

N° pazienti con entrambi i genitori portatori: 3



## ORIGINAL ARTICLE

# Cryptic deletions are a common finding in “balanced” reciprocal and complex chromosome rearrangements: a study of 59 patients

M De Gregori, R Ciccone, P Magini, T Pramparo, S Gimelli, J Messa, F Novara, A Vetro, E Rossi, P Maraschio, M C Bonaglia, C Anichini, G B Ferrero, M Silengo, E Fazzi, A Zatterale, R Fischetto, C Previderé, S Belli, A Turci, G Calabrese, F Bernardi, E Meneghelli, M Riegel, M Rocchi, S Gueneri, F Lalatta, L Zelante, C Romano, Ma Fichera, T Mattina, G Arrigo, M Zollino, S Giglio, F Lonardo, A Bonfante, A Ferlini, F Cifuentes, H Van Esch, L Backx, A Schinzel, J R Vermeesch, O Zuffardi

## ORIGINAL ARTICLE

# A novel microdeletion syndrome at 3q13.31 characterised by developmental delay, postnatal overgrowth, hypoplastic male genitals, and characteristic facial features

A-M Molin,<sup>1</sup> J Andrieux,<sup>2</sup> D A Koolen,<sup>3</sup> V Malan,<sup>4</sup> M Carella,<sup>5</sup> L Colleaux,<sup>4</sup> V Cormier-Daire,<sup>4</sup> A David,<sup>6</sup> N de Leeuw,<sup>3</sup> B Delobel,<sup>7</sup> B Duban-Bedu,<sup>7</sup> R Fischetto,<sup>8</sup> F Flinter,<sup>9</sup> S Kjaergaard,<sup>10</sup> F Kok,<sup>11</sup> A C Krepischi,<sup>12,13</sup> C Le Caignec,<sup>6,14</sup> C Mackie Ogilvie,<sup>15</sup> S Maia,<sup>16</sup> M Mathieu-Dramard,<sup>17</sup> A Munnich,<sup>4</sup> O Palumbo,<sup>5</sup> F Papadia,<sup>8</sup> R Pfundt,<sup>3</sup> W Reardon,<sup>18</sup> A Receveur,<sup>19</sup> M Rio,<sup>4</sup> L Ronsbro Darling,<sup>20</sup> C Rosenberg,<sup>12</sup> J Sá,<sup>16</sup> L Vallee,<sup>21</sup> C Vincent-Delorme,<sup>22</sup> L Zelante,<sup>5</sup> M-L Bondeson,<sup>1</sup> G Annerén<sup>1</sup>

► Additional materials are published online only. To view these files please visit the journal online (<http://jmg.bmj.com/content/43/2.toc>).

For numbered affiliations see end of article.

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Received 28 September 2011  
Revised 10 November 2011  
Accepted 18 November 2011  
Published Online First  
17 December 2011

**ABSTRACT**

**Background** Congenital deletions affecting 3q11q23 have rarely been reported and only five cases have been molecularly characterised. Genotype–phenotype correlation has been hampered by the variable sizes and breakpoints of the deletions. In this study, 14 novel patients with deletions in 3q11q23 were investigated and compared with 13 previously reported patients.

**Methods** Clinical data were collected from 14 novel patients that had been investigated by high resolution microarray techniques. Molecular investigation and updated clinical information of one cytogenetically previously reported patient were also included.

**Results** The molecular investigation identified deletions in the region 3q12.3q21.3 with different boundaries and variable sizes. The smallest studied deletion was 580 kb, located in 3q13.31. Genotype–phenotype comparison in 24 patients sharing this shortest region of overlapping deletion revealed several common major characteristics including significant developmental delay, muscular hypotonia, a high arched palate, and recognisable facial features including a short philtrum and protruding lips. Abnormal genitalia were found in the majority of males, several having micropenis. Finally, a postnatal growth pattern above the mean was apparent. The 580 kb deleted region includes five RefSeq genes and two of them are strong candidate genes for the developmental delay: *DRO3* and *ZBTB20*.

**Conclusion** A newly recognised 3q13.31 microdeletion syndrome is delineated which is of diagnostic and prognostic value. Furthermore, two genes are suggested to be responsible for the main phenotype.

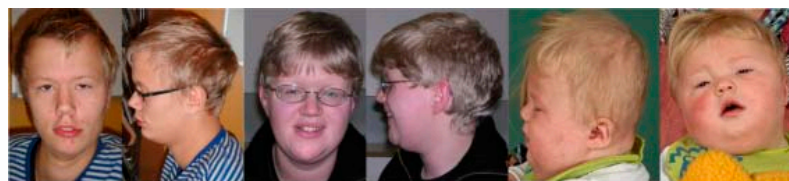
**INTRODUCTION**

Deletions affecting the proximal long arm of chromosome 3 are rarely reported in the literature. Hitherto, 14 patients have been described with deletions of various sizes and different breakpoints within the 3q11q23 region. The deletions were investigated in nine of the patients by standard

karyotyping<sup>1–8</sup> and only five cases have been investigated by molecular methods.<sup>9–14</sup> The 14 patients had a range of different phenotypes including cranial and facial dysmorphisms, developmental retardation, and genital and peripheral musculoskeletal abnormalities. However, determining a proper genotype–phenotype correlation has been hampered by the few cases with molecularly defined deletions as well as by the limited number of patients described.

The advent of high resolution microarray techniques has greatly facilitated the investigation of chromosomal disorders, enabling the identification of disease-causative genes for known syndromes—for example, CHARGE syndrome (OMIM 214800) and 9q subtelomeric deletion syndrome (OMIM 610253) as reviewed in Vissers *et al.*<sup>15</sup> In addition, a number of novel microdeletion and micro-duplications syndromes have been delineated, starting with the first described 17q21.31 microdeletion syndrome in 2006 (reviewed in Vissers *et al.*<sup>15</sup>). Moving from a cytogenetic approach to an ever more sensitive molecular karyotyping has reversed the strategy behind the identification of novel syndromes—that is, patients having similar/overlapping genetic rearrangements are identified before the clinical characteristics of a syndrome are defined. Furthermore, the collection of clinical and genetic information in databases such as DECIPHER,<sup>16</sup> ISCA,<sup>17</sup> and ECARUCA<sup>18</sup> has been crucial for the comparison between patients with rare aberrations.

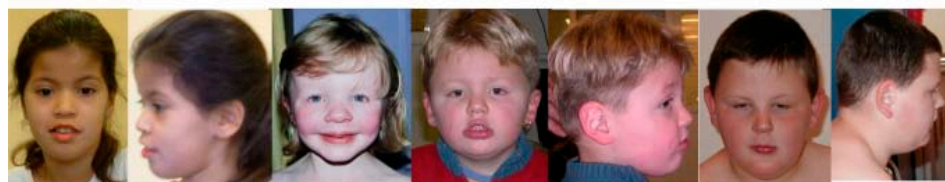
Using a reverse genetics approach and a joint collaborative effort through DECIPHER, we describe 14 novel patients carrying microscopic or submicroscopic deletions in the region 3q12.3q21.3. In addition, a molecular investigation is presented of a previously reported 3q-deletion patient.<sup>9</sup> This study also presents a review of the 13 previously reported patients. A newly recognised 3q13.31 microdeletion syndrome is identified, characterised by developmental delay, postnatal growth above



Case 1

Case 2

Case 4

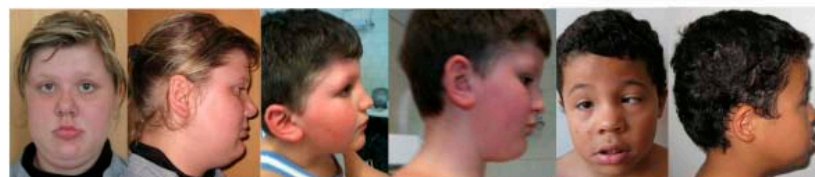


Case 5

Case 6

Case 7

Case 9



Case 10

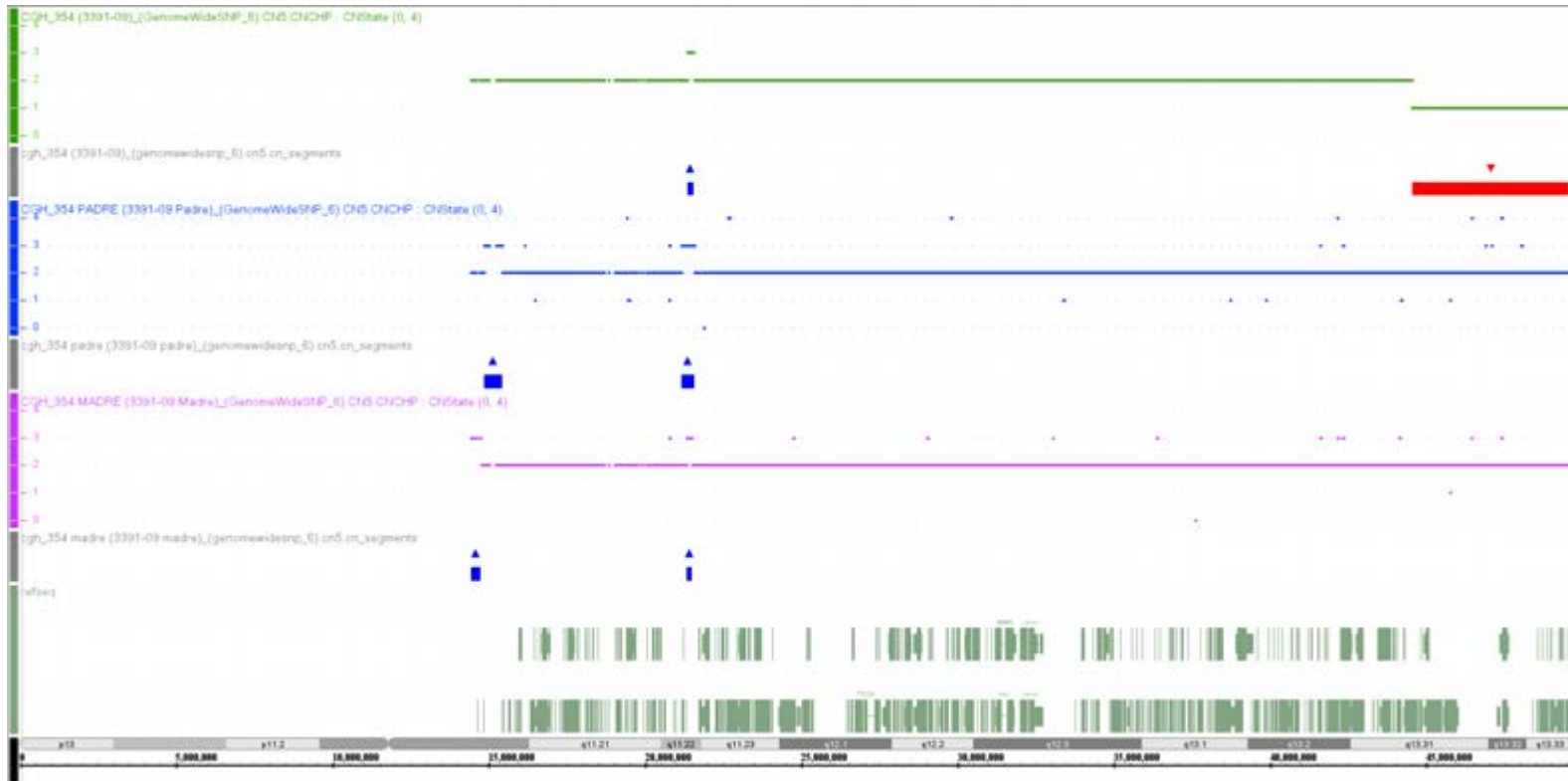
Case 12

Case 15



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://jmg.bmj.com/site/about/unlocked.xhtml>

G. G.: del22q13.3q13.33 (44558201-49581309; 5 Mb), de novo.



- OMIM GENES: ATXN10, PPARA, TRMU, ALG12, MLC1, SCO2, TYMP, ARSA, **SHANK3**, ACR;
- **22q13 deletion Syndrome** (Phelan-Mcdermid syndrome).

RESEARCH ARTICLE

AMERICAN JOURNAL OF  
medical genetics PART  
A

**22q13.3 Deletion Syndrome: Clinical and Molecular Analysis Using Array CGH**

G. G.: del22q13.3q13.33 (44558201-49581309; 5 Mb), de novo.

## Clinical characteristics of deletion 22q13 syndrome

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### **Occurring in >95%**

Severe global developmental delay  
Absent/severe speech delay  
Hypotonia  
Normal/accelerated growth

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### **Occurring in >75%**

Long eye lashes  
Prominent, dysplastic ears  
Relatively large, fleshy hands  
Hypoplastic/dysplastic toenails  
Decreases sensitivity to pain

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### **Occurring in >50%**

Dolicocephaly  
Full brow  
Prominent/dysplastic ears  
Full/puffy cheeks  
Full/puffy eyelids  
Pointed chin  
Deep set eyes  
Ptosis  
Decreased perspiration/tendency to overheat  
Flat midface  
Wide nasal bridge  
Bulbous nose  
Sacral dimple

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### **Occurring in >25%**

Cyclic vomiting  
Strabismus  
Epicanthal folds  
Wide spaced teeth/malocclusion  
2–3 syndactyly of the toes  
Fifth finger clinodactyly  
Seizures  
Lymphedema  
Gastroesophageal reflux  
Renal abnormalities

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### **Occurring in <25%**

Hearing loss (~20%)  
Arachnoid cyst (~15%)  
Cellulitis (~10%)

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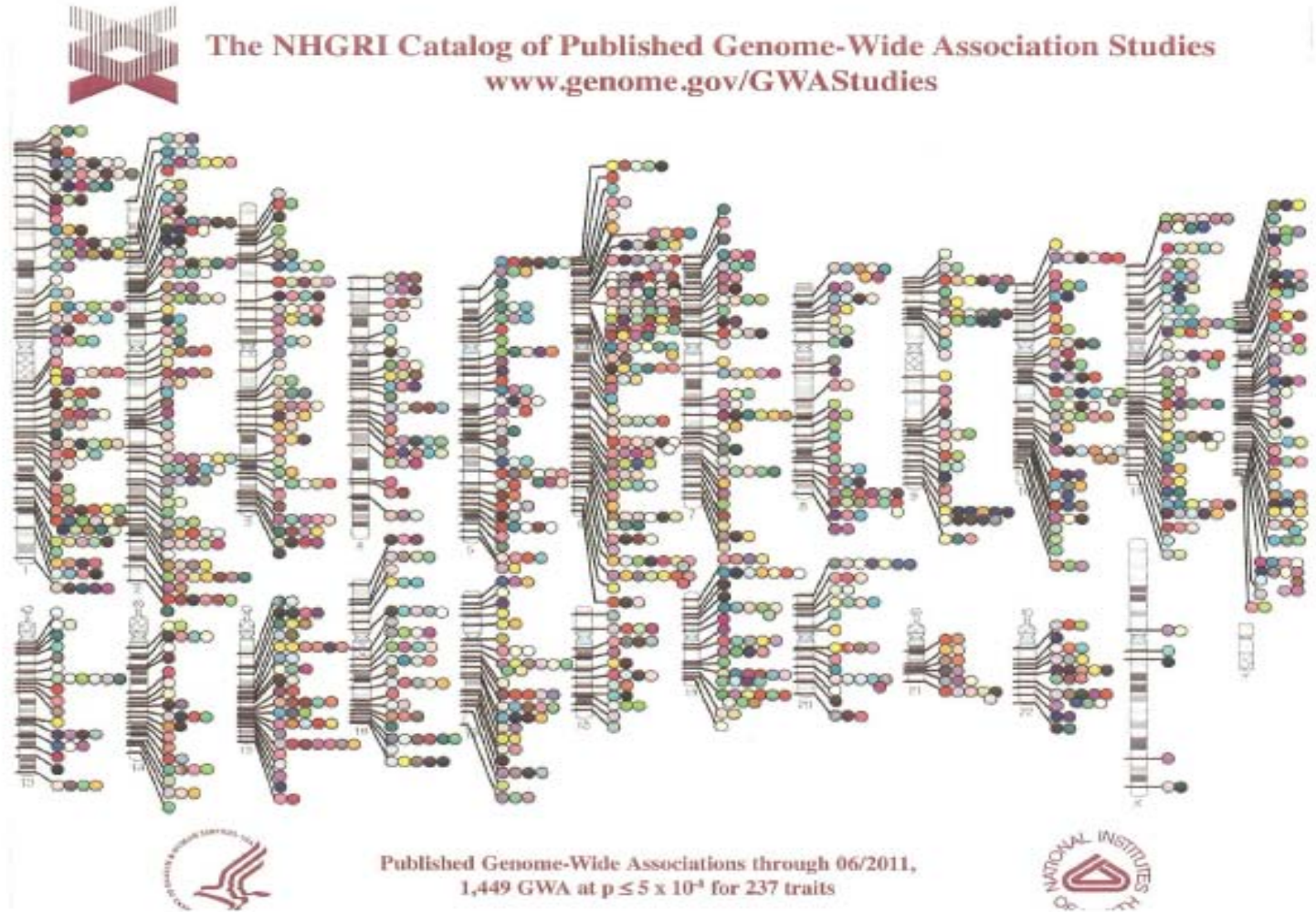
### **Behavioral features**

Poor eye contact  
Stereotypic movements  
Decreased socialization  
Language impairment  
Chewing/mouthing of non-food items (80–90%)  
Teeth grinding (about 25%)  
Tongue thrusting (about 15%)  
Aggressive behavior (10–15%)

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# Malattie complesse- multifattoriali e tratti quantitativi:

## GWAS studies



# Elenco dei tratti studiati e numero di associazione trovate (giugno, 2011):



Diabete, asma, psoriasi, artrite,

Peso, altezza, colesterolo, pressione arteriosa

**EPIGENETICA: cambiamenti ereditari dell'espressione genica che, a differenza delle mutazioni, non sono attribuibili ad alterazioni della sequenza del DNA.**

## **“MARKERS MISURABILI” DELLE INFLUENZE AMBIENTALI**

- **Meccanismi: metilazione del DNA, modifiche struttura della CROMATINA, perdita dell'Imprinting ed RNA non codificante con effetti a lungo termine e ad ampio raggio**
- **Farmaci, alimentazione, alcool, fumo, droghe, dismetabolismi, patologie croniche : gameti / cellule embrionarie (fase pre-impianto precoce) / cellule somatiche**

**“Life style” e rischio di malattia**

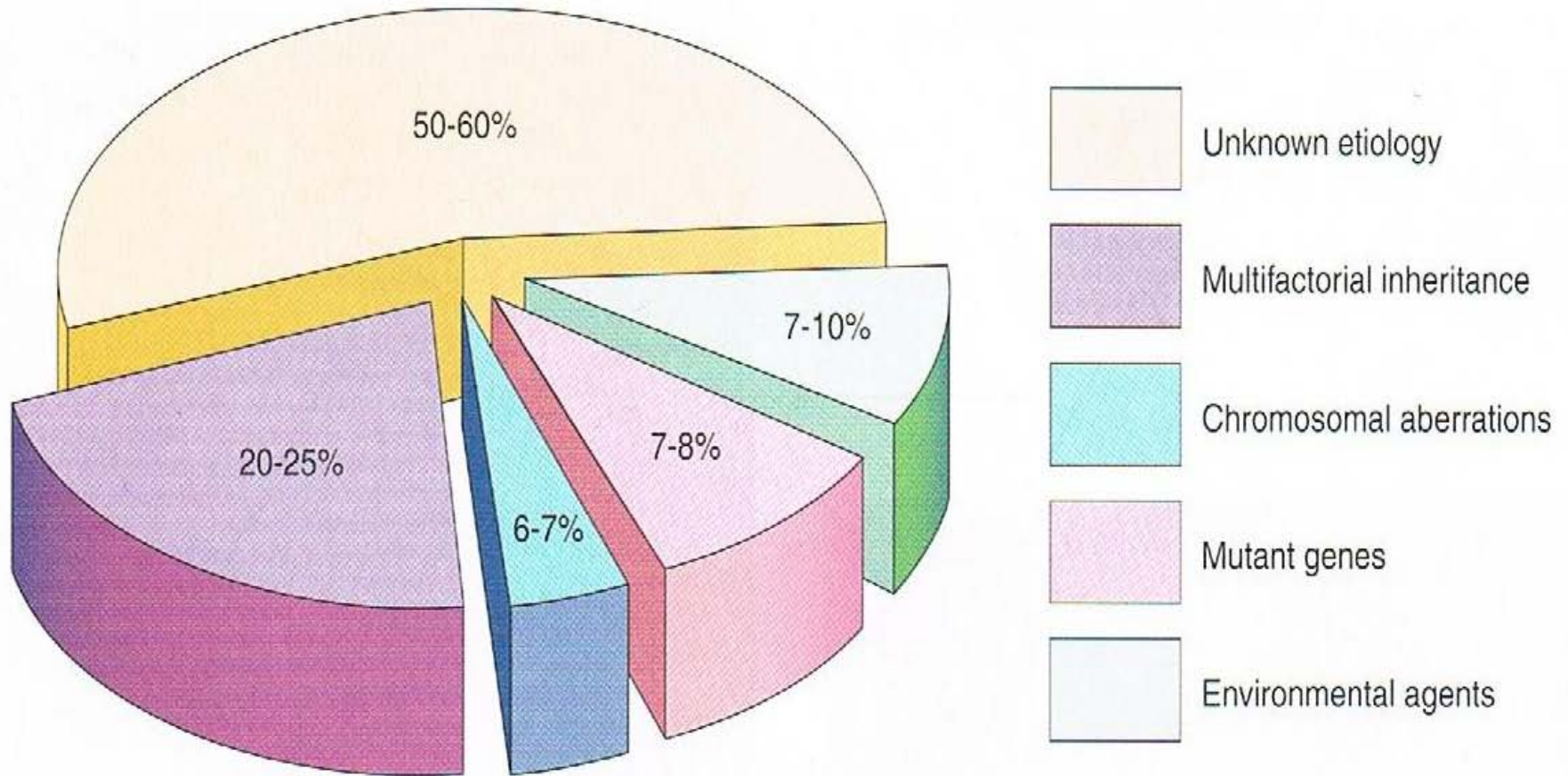
# EMERGENZA di malattie legate all'eccessiva introduzione di calorie e nutrienti “EPIDEMIA” OBESITÀ E DIABETE

## Questione di GUSTO



Potere educativo della persuasione: che cosa funziona di più?





**Figure 8-1.** Graphic illustration of the causes of human birth defects. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).

# Educazione genetica

- La Genetica Clinica può essere già parte della Medicina/ Pediatria Generale
- Filtro clinico nella SELEZIONE del test **idoneo** per la patologia sospettata ed interpretazione
- Sorveglianza

# Regione Puglia

Realtà già operativa/ in corso di organizzazione:

- Registro Regionale Malattie Rare e Rete di assistenza ;
- Progetto Nardino: modello assistenziale di gestione diagnostica e presa in carico Pz. con patologia cronica
- Screening neonatale allargato Malattie Metaboliche

# Regione Puglia

Ipotesi di lavoro:

- nuovo paradigma nel rapporto medico-paziente
- personalizzare la medicina e gli stili di vita
- capillarizzare le conoscenze
- istituire un ambulatorio per il “ COUNSELING PRECONCEZIONALE” dei difetti congeniti



# **“Tendenze demografiche, cambiamenti tecnologici e crescita economica nei paesi avanzati”**

L. Bini Smaghi (“Area pediatrica “ 2011)

## **SOCIETÀ AVANZATE**

tendenza demografica limitata

progresso tecnologico

capitale umano (e di salute)

livello di istruzione / apprendistato

## **PREPARARE I GIOVANI**

### **Pediatra / Medico Generale**

lavoro scientifico+ pratica:contribuisce ad allungare durata/qualità vita





**Quello che mi ha sorpreso di più degli uomini dell'Occidente è che perdono la salute per fare i soldi, e poi perdono i soldi per fare la salute.**

**Pensano tanto al futuro che dimenticano di vivere il presente in tale maniera che non riescono a vivere né il presente né il futuro. Vivono come se non dovessero morire mai e muoiono come se non avessero mai vissuto.**

**Dalai lama**

**GRAZIE!**