MALATTIE RARE
CONOSCERLE PER RICONOSCERLE
Castellaneta Marina (TA), 18-19 maggio 2012

amegep
Domenico Campanella
associazione malattie metaboliche e genetiche puglia
O.N.L.U.S
info@amegepdomenicocampanella.it

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

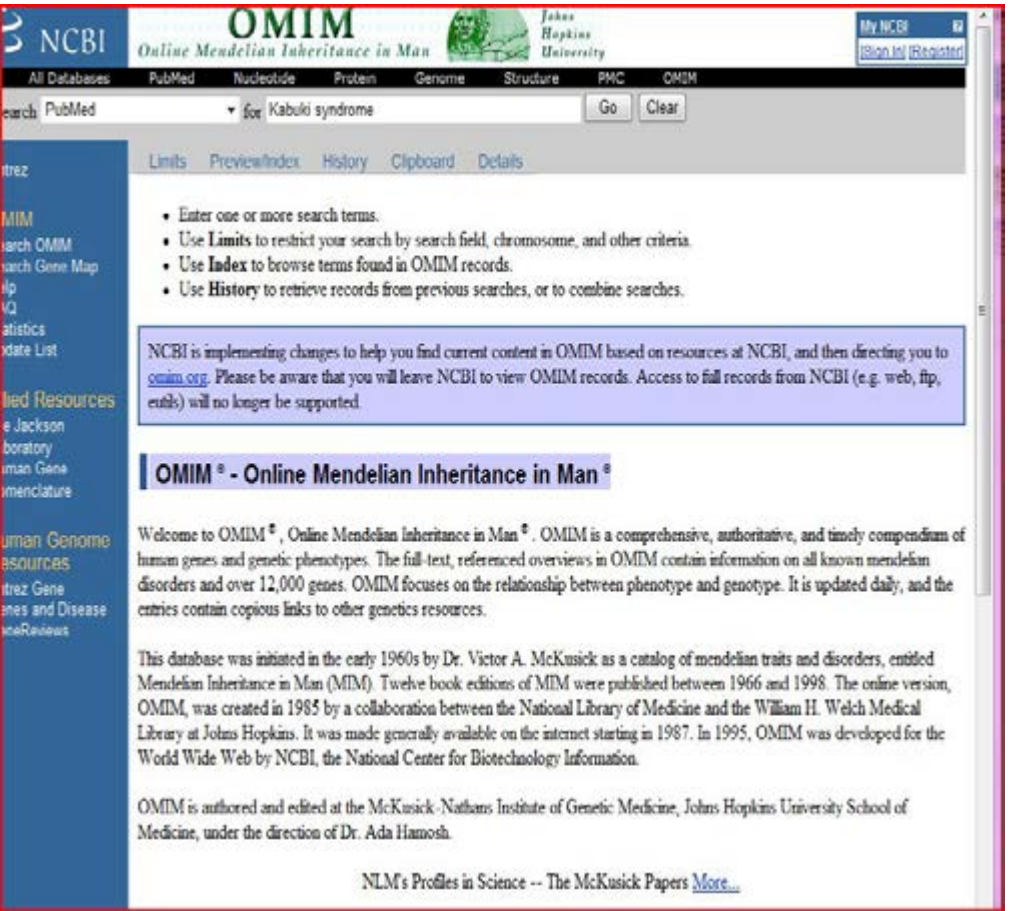
Rita Fischetto
Referente Genetica Clinica
U.O.C. Malattie Metaboliche Diabetologia
A.O.U. Policlinico-Giovanni XXIII
Bari

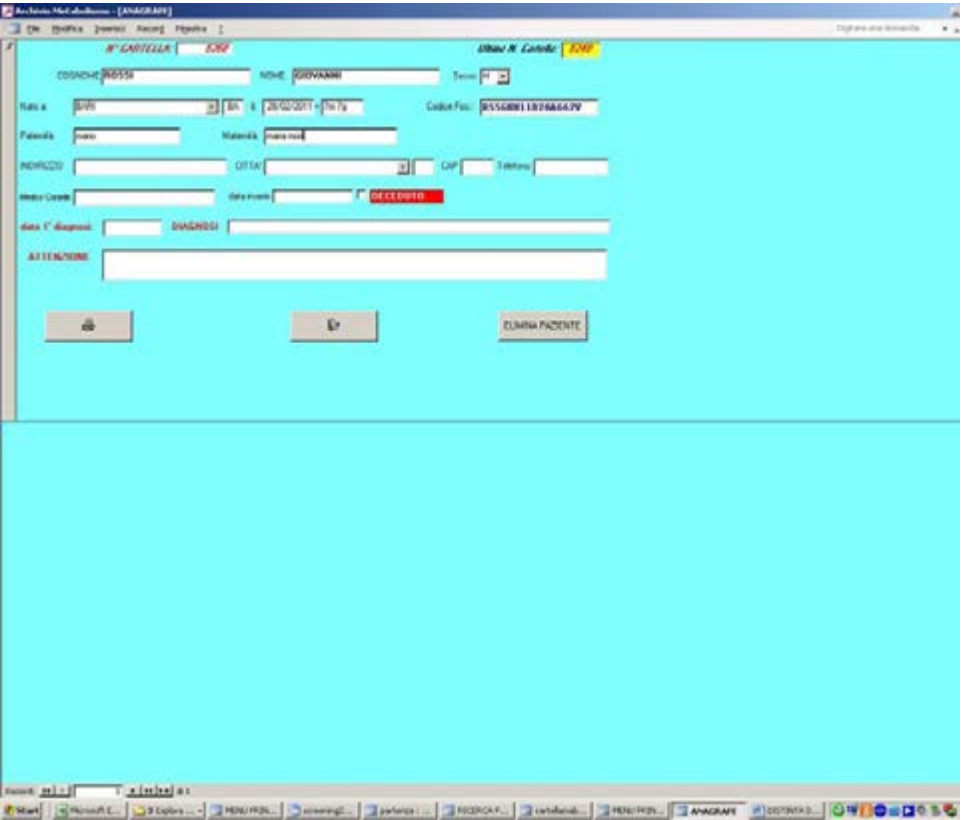
SIMGePeD

Società Italiana di Pediatria

Policlinico di Bari
Ospedale Giovanni XXIII

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





Fenilchetonuria	196
S. Down	126
Neurofibromatosi	115
Aneuploidie altri cromosomi	64
S. Marfan	61
OA ; AApatie; 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

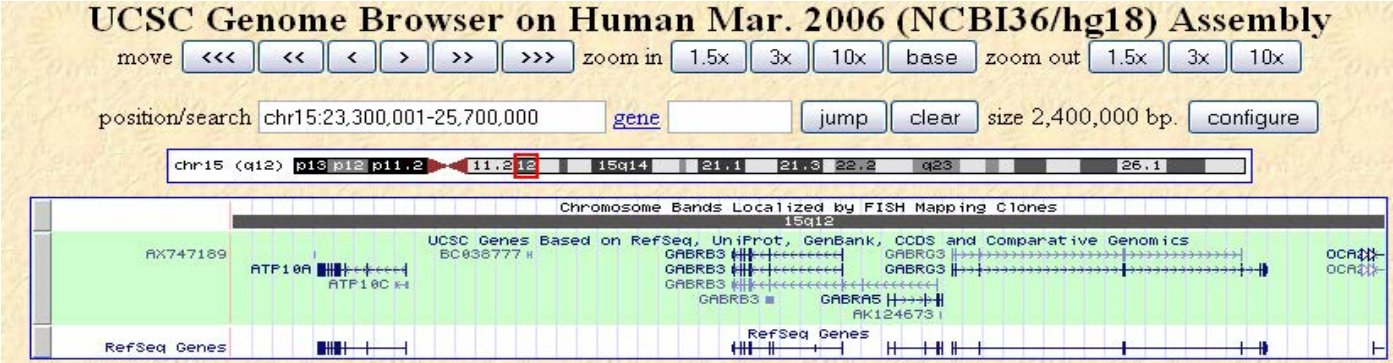
Epigenetica

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, SGuerneri, 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

J Med Genet 2007;**44**:750–762. doi: 10.1136/jmg.2007.052787

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

► Additional materials are published online only. To view these files please visit the journal online (http://jmg.bmj.com/content/49/2.toc).

For numbered affiliations see end of article.

Correspondence to
Dr Anna-Maja Molin, Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Science for Life Laboratory, Uppsala 75237, Sweden; anna-maja.nystrom@slu.se

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UNLOCKED

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

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: *DRD3* 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

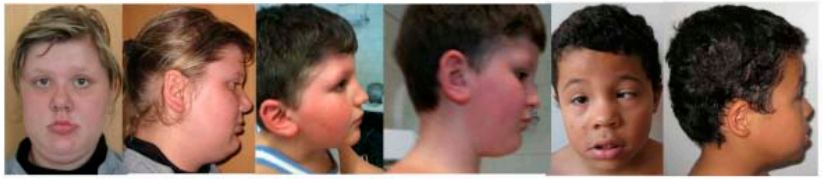
Deletions affecting the proximal long arm of chromosome 3 are rarely reported in the literature. Hitherto, 14 patients have been described with deletions of various sizes and different breakpoints within the 3q11q23 region. The deletions were investigated in nine of the patients by standard karyotyping[1–8] and only five cases have been investigated by molecular methods.[9–14] 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*.[15] In addition, a number of novel microdeletion and microduplications syndromes have been delineated, starting with the first described 17q21.31 microdeletion syndrome in 2006 (reviewed in Vissers *et al*[15]). 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,[16] ISCA,[17] and ECARUCA[18] 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.[5] 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

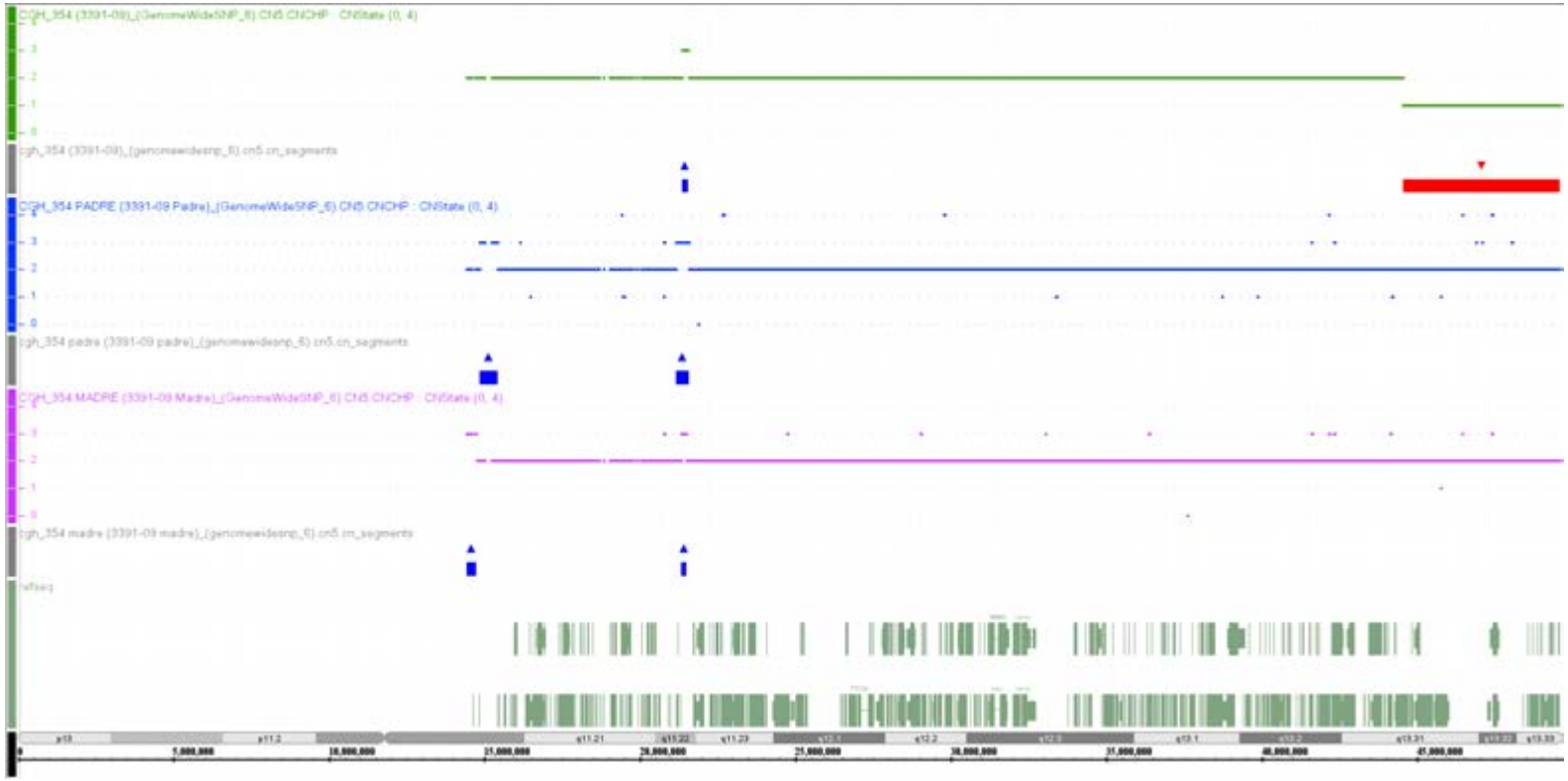
Case 5 Case 6 Case 7 Case 9



Case 10 Case 12 Case 15

J Med Genet 2012;49:104–109. doi:10.1136/jmedgenet-2011-100534

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

Occurring in >95%
Severe global developmental delay
Absent/severe speech delay
Hypotonia
Normal/accelerated growth

Occurring in >75%
Long eye lashes
Prominent, dysplastic ears
Relatively large, fleshy hands
Hypoplastic/dysplastic toenails
Decreases sensitivity to pain

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

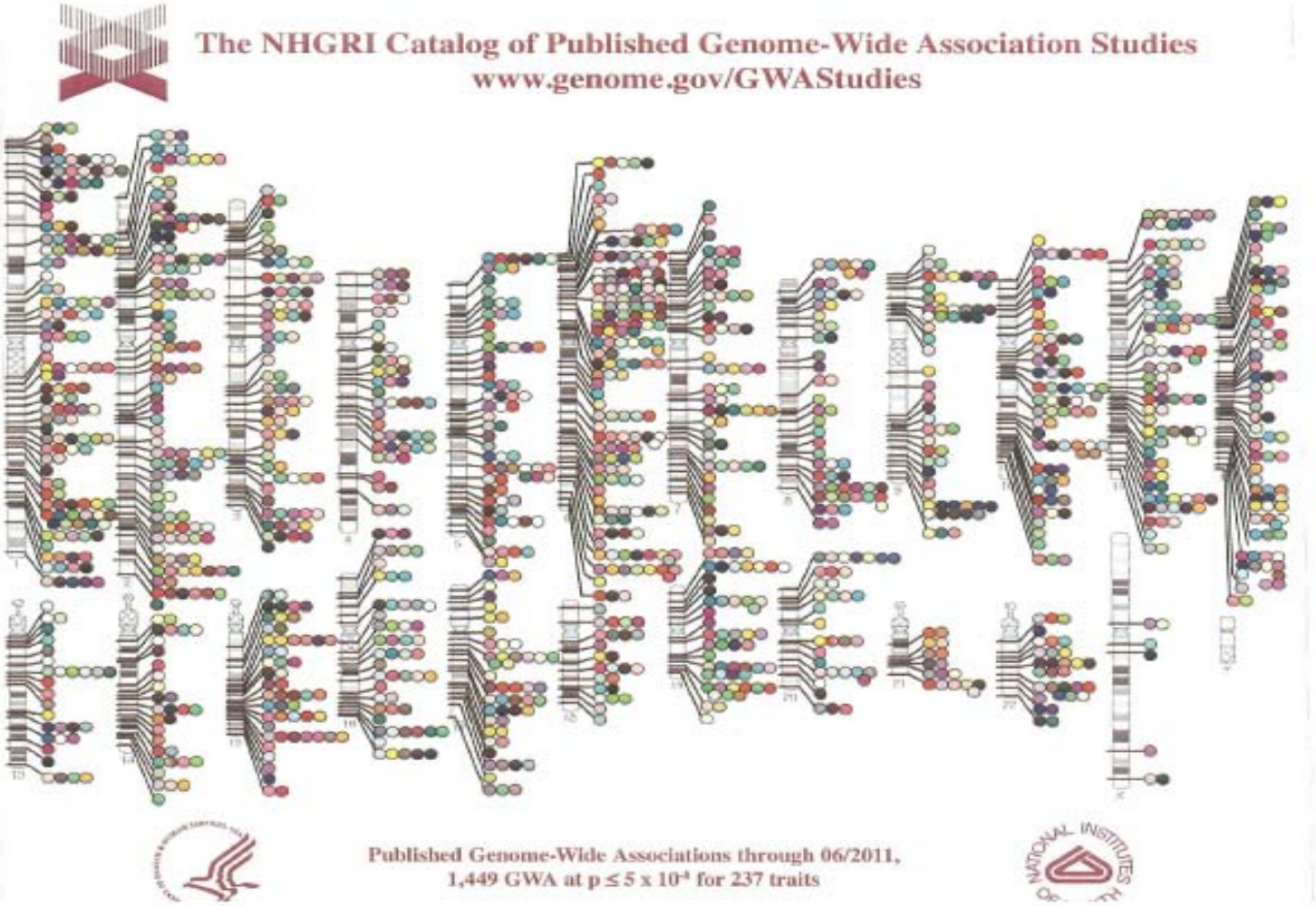
Occurring in >25%
Cyclic vomiting
Strabismus
Epicanthal folds
Wide spaced teeth/malocclusion
2–3 syndactyly of the toes
Fifth finger clinodactyly
Seizures
Lymphedema
Gastroesophageal reflux
Renal abnormalities

Occurring in <25%
Hearing loss (~20%)
Arachnoid cyst (~15%)
Cellulitis (~10%)

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%)

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?

Moore Persaud, 2003

Human Birth Defects

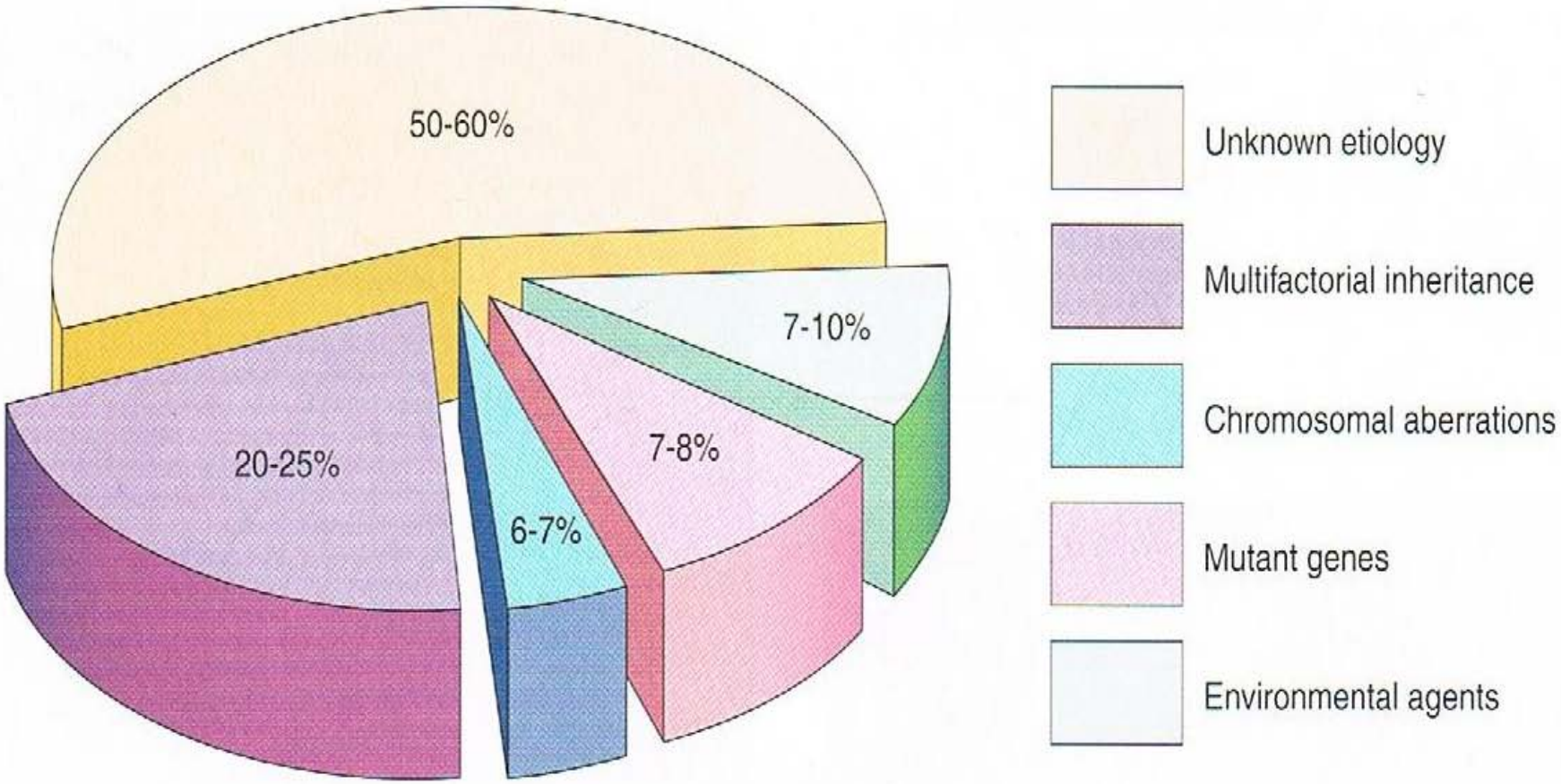


Figure 8-1. Graphic illustration of the causes of human birth defects. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).

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 gia 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!