PRIMO CONVEGNO NAZIONALE ASSOCIAZIONE ANOMALIE CORPO CALLOSO

22 – 23 SETTEMBRE 2012

Background genetico e *work-up* diagnostico dell'agenesia del corpo calloso

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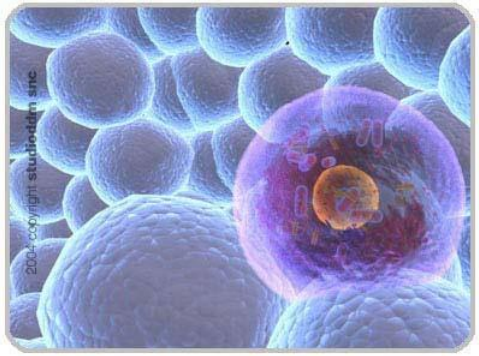
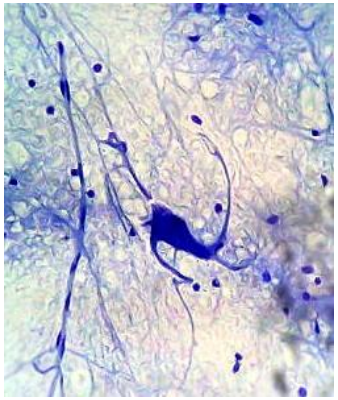
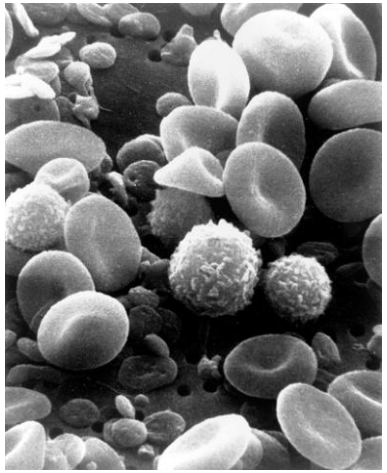
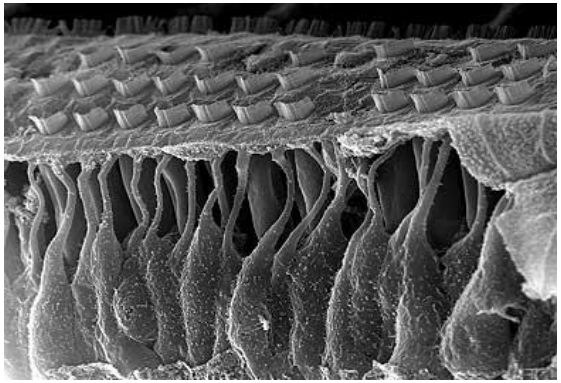
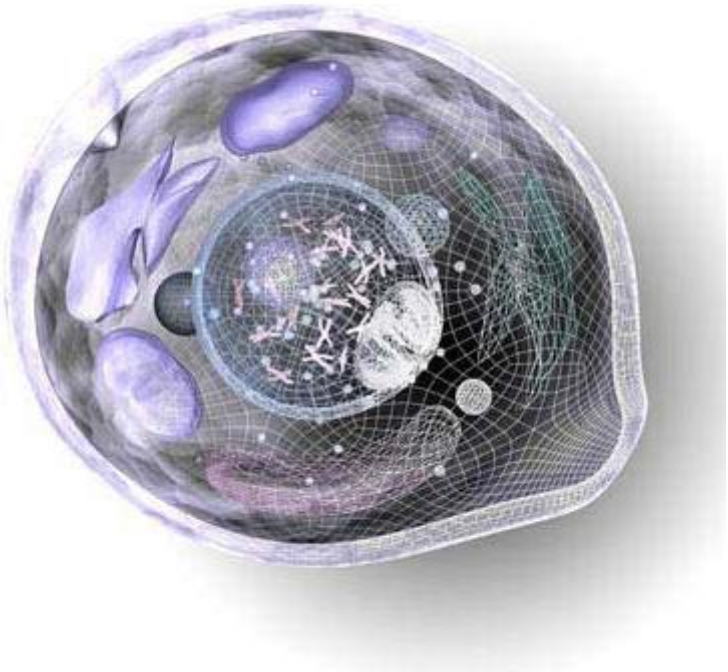


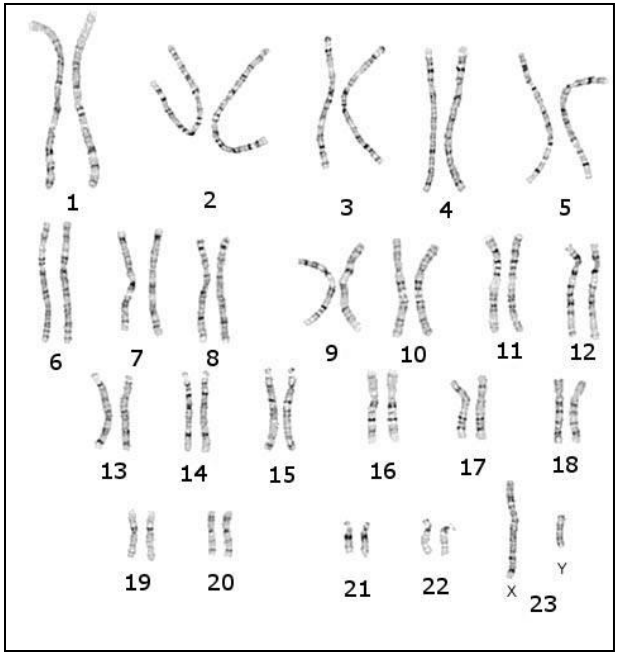


100 000 miliardi (10^{14})
di cellule





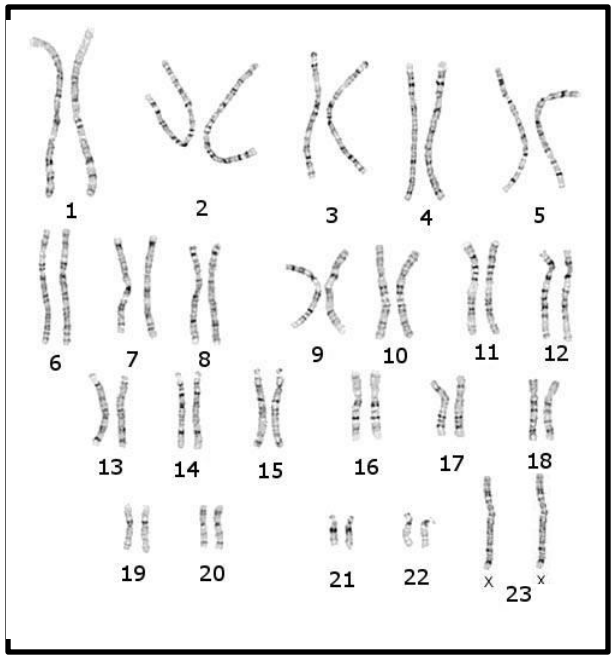




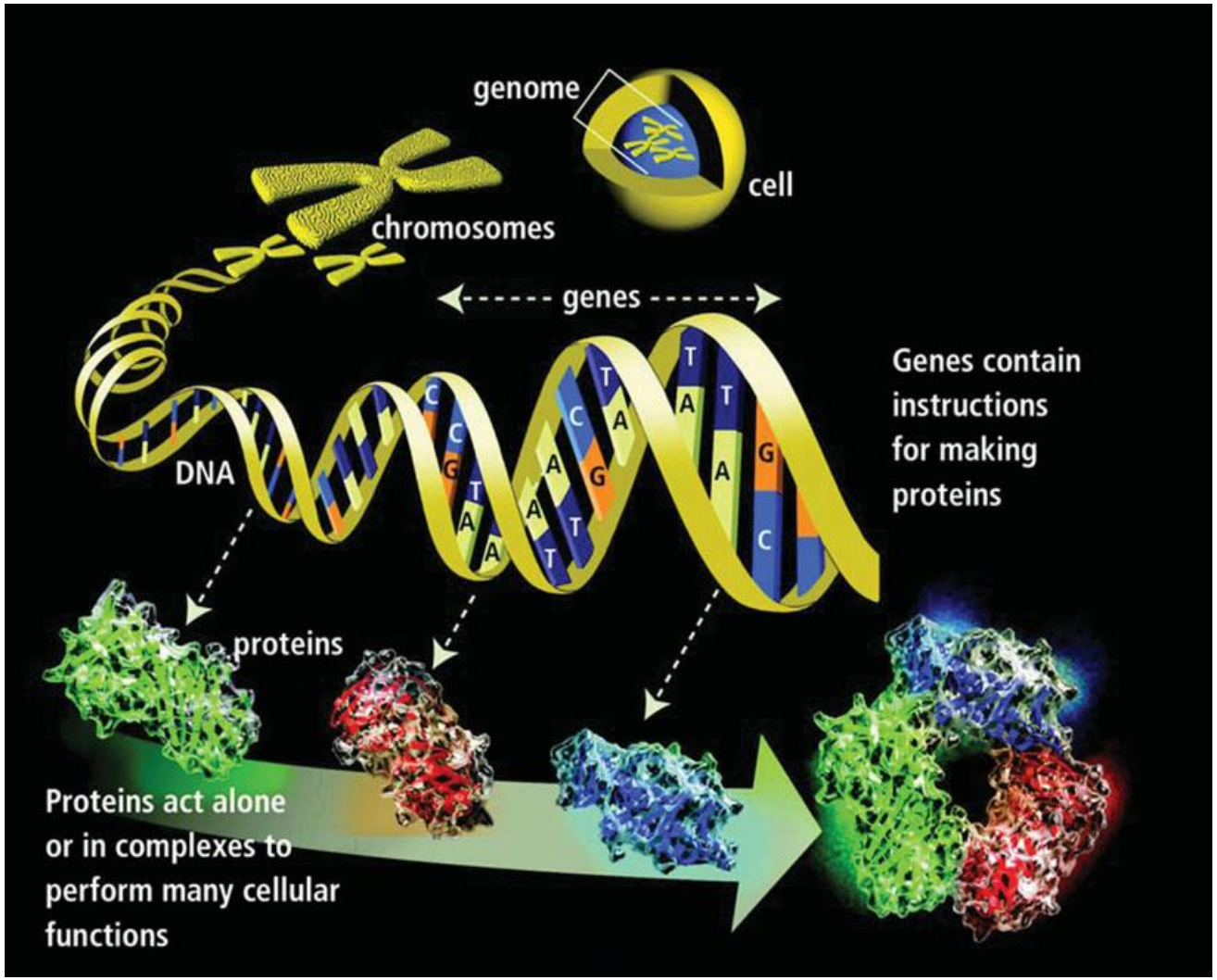
46 cromosomi

23 di origine paterna

23 di origine materna



30000 geni in duplice copia
(1/3 espressi anche o solo nell'encefalo)

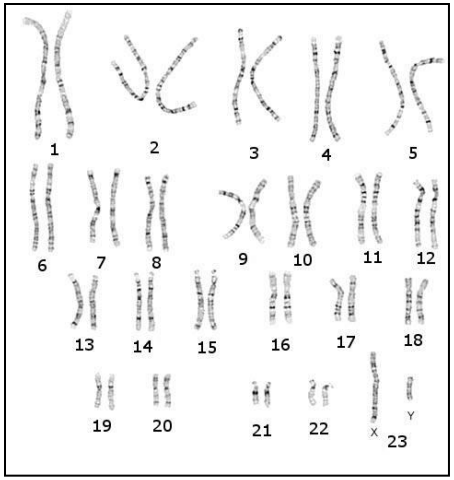


Anomalie genetiche

- **Cromosomiche** (di numero, di struttra)

- **Geniche** (nella sequenza del DNA)

Anomalie cromosomiche numeriche



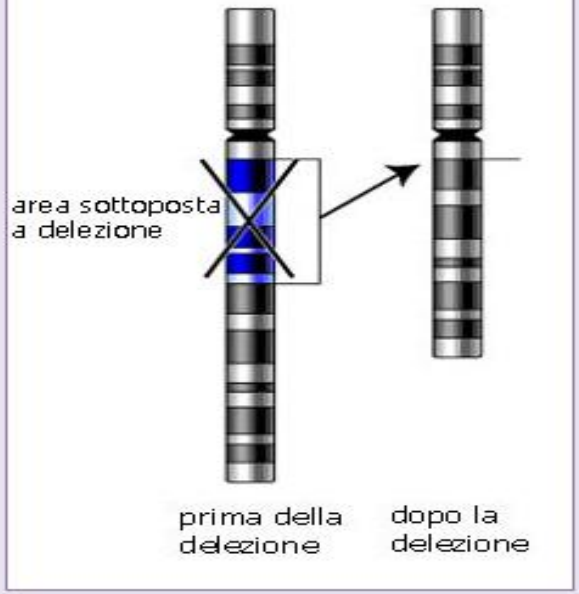
Aneuploidia: il termine aneuploidia descrive la situazione anormale in cui uno o una coppia di cromosomi vengono persi o aggiunti rispetto all'assetto cromosomico normale (2N). Si parla di nullisomia quando si ha la perdita di un paio di cromosomi omologhi (2N-2); monosomia quando si ha la perdita di un singolo cromosoma (2N-1); trisomia implica un singolo cromosoma in più, vale a dire che la cellula ha tre copie per un cromosoma e due copie di ogni altro paio (2N+1); tetrasomia quando si hanno quattro cromosomi omologhi (2N+2).

Monoploidia: implica variazioni rispetto alla condizione normale (2N), del numero di interi assetti cromosomici. Un individuo monoploide presenta un solo assetto cromosomico (N). Si verifica raramente.

Poliploidia: si verifica quando un individuo possiede un numero di assetti cromosomici superiore al normale. Una cellula con tre assetti cromosomici è definita triploide (3N),con quattro, tetraploide (4N).

Anomalie cromosomiche di struttura

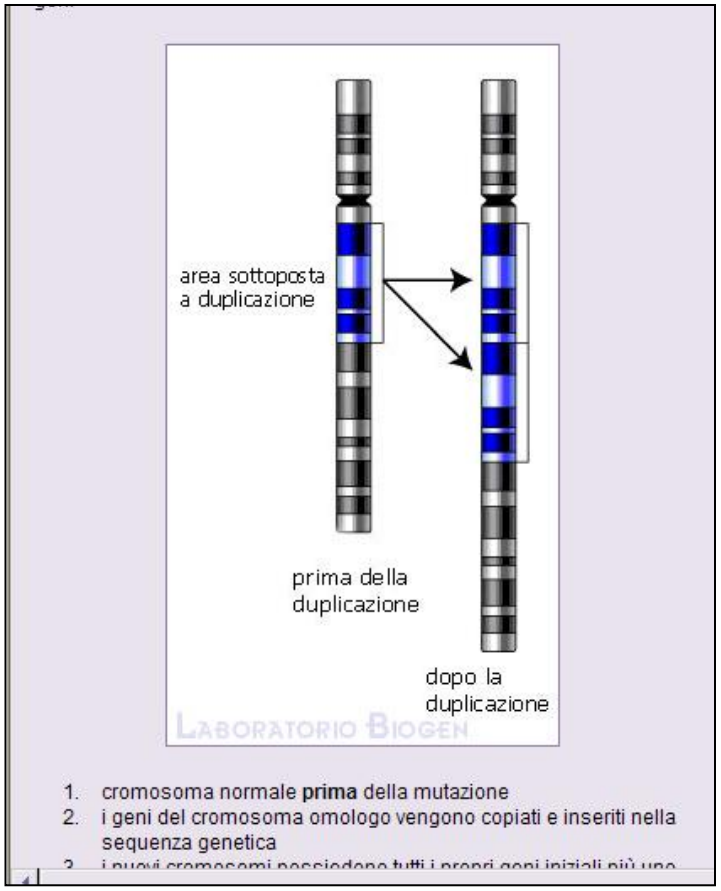
1. **Delezioni:** comportano un cambiamento nella quantità di materiale genetico di un cromosoma e provocano, come conseguenza, la perdita di un tratto di materiale genetico e della relativa informazione in esso contenuta. Il segmento deleto può essere localizzato in un punto qualsiasi lungo il cromosoma



1. cromosoma normale **prima** della mutazione
2. i geni non attaccati al centromero si staccano e sono irrimediabilmente persi
3. ai nuovi cromosomi mancano alcuni geni che potrebbero rivelarsi fatali in funzione della loro importanza

Anomalie cromosomiche di struttura

2. **Duplicazioni:** comportano un cambiamento nella quantità di materiale genetico di un cromosoma per raddoppiamento di un tratto di esso.
Le duplicazioni possono essere o non essere letali per un individuo.
La dimensione del tratto duplicato può variare in modo considerevole e segmenti duplicati possono trovarsi in punti diversi del cromosoma o uno vicino all'altro



Anomalie geniche: mutazioni

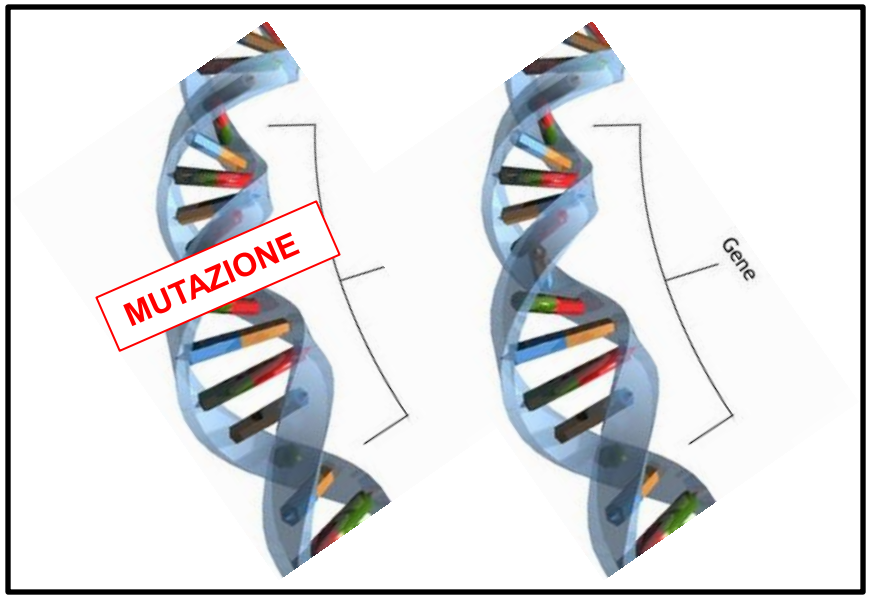
Alterano la sequenza del DNA

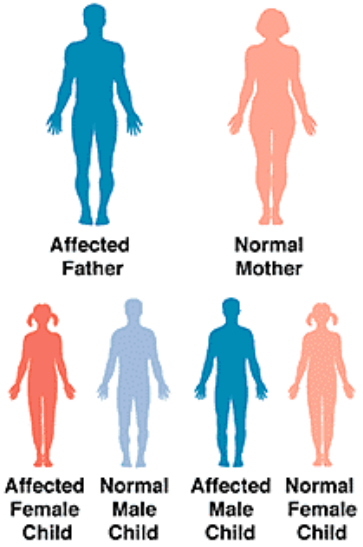
- **Sostituzioni:** una coppia di basi nel DNA è sostituita da un'altra coppia
- **Inserzioni:** consistono nell'acquisizione di una o più coppie di basi
- **Delezioni:** consistono nella perdita di una o più coppie di basi

Trasmissione ereditaria dei caratteri mendeliani

- Eredità autosomico dominante (AD) -

- Un individuo affetto possiede un'alterazione in una sola copia di uno specifico gene,
- Un individuo affetto ha comunemente almeno un genitore affetto,
- La patologia si manifesta in uguale misura nei due sessi
- Un figlio di una persona affetta e di una persona non affetta ha il 50% di probabilità di essere affetto

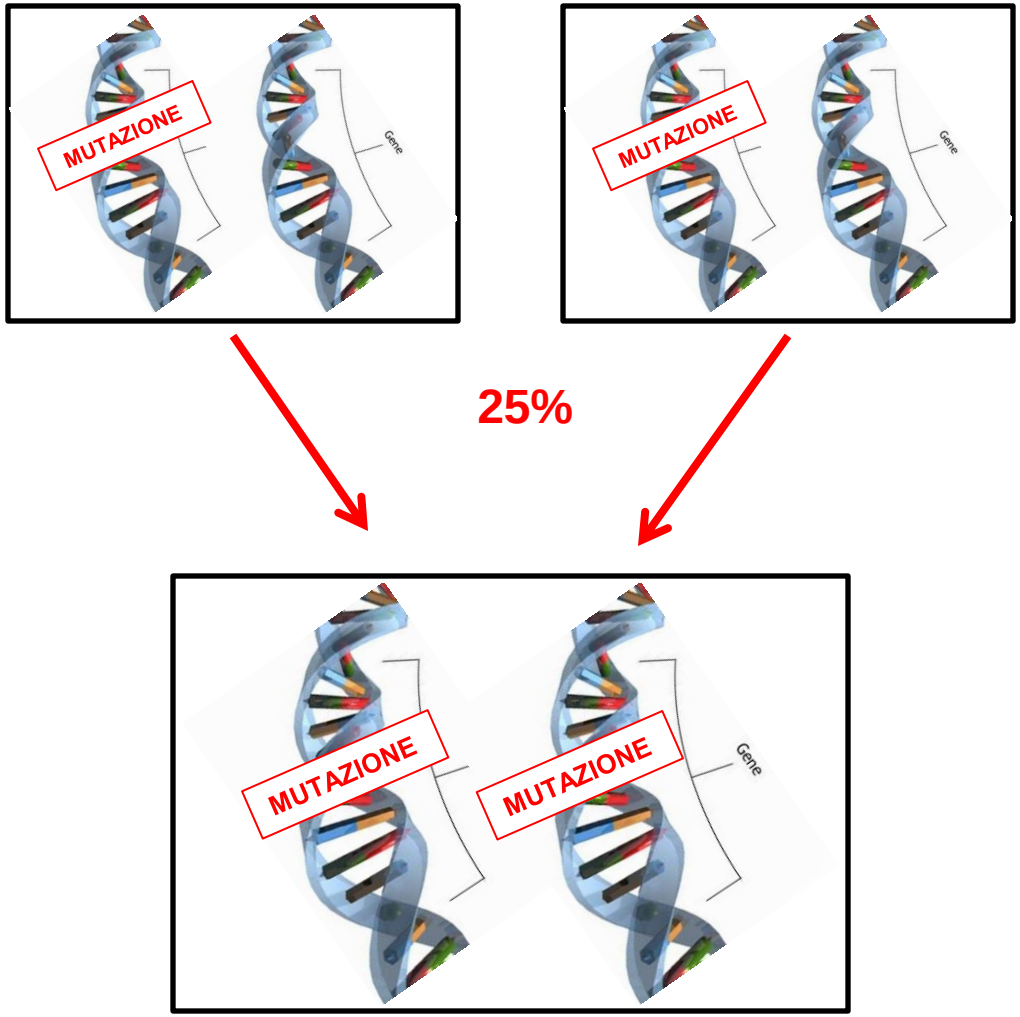




Trasmissione ereditaria dei caratteri mendeliani

- Eredità autosomico recessiva (AR) -

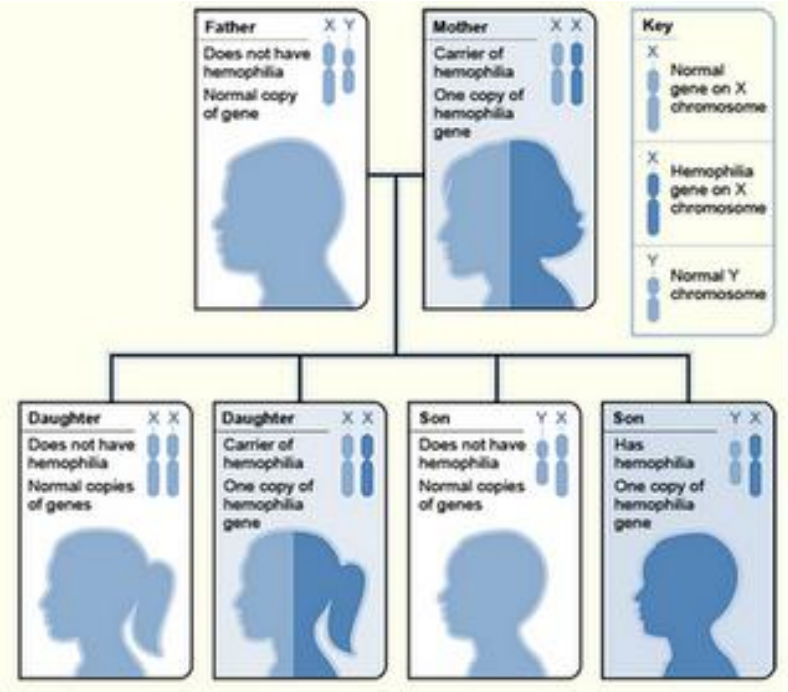
- Un individuo affetto possiede un'alterazione in entrambe le copie di uno specifico gene (omozigote)
- Solitamente entrambi i genitori sono portatori eterozigoti di una mutazione e generalmente asintomatici
- La patologia si manifesta in uguale misura nei due sessi
- Una coppia di portatori sani avrà il 25% di probabilità di concepire un figlio affetto, il 50% di probabilità di avere un figlio portatore sano ed il 25% di probabilità di avere un figlio genotipicamente normale

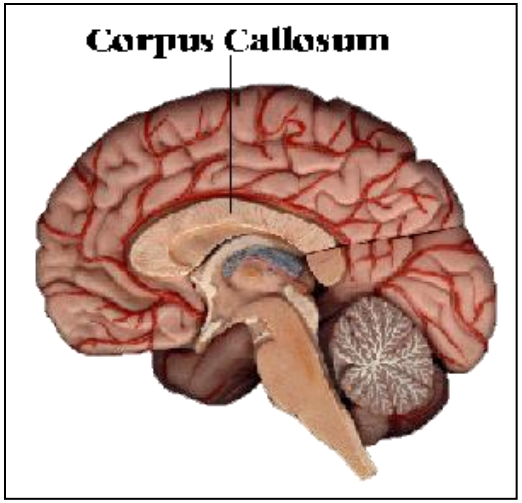


Trasmissione ereditaria dei caratteri mendeliani

- Eredità X-Linked (XL) -

- Solo i maschi manifestano la patologia dal momento che ereditano, dalla madre generalmente sana, un difetto genico localizzato sul cromosoma X.
- Le donne portatrici di un difetto genico sul cromosoma X avranno, ad ogni gravidanza, una probabilità pari al 50% di trasmettere lo stesso difetto ai figli maschi che saranno affetti ed una probabilità pari al 50% di avere figlie femmine a loro volta portatrici (sane) del difetto genico materno.





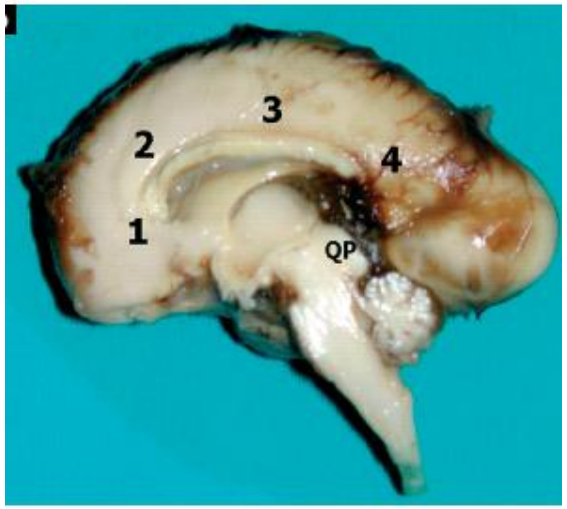
Il corpo calloso è la principale commissura che collega i due emisferi cerebrali

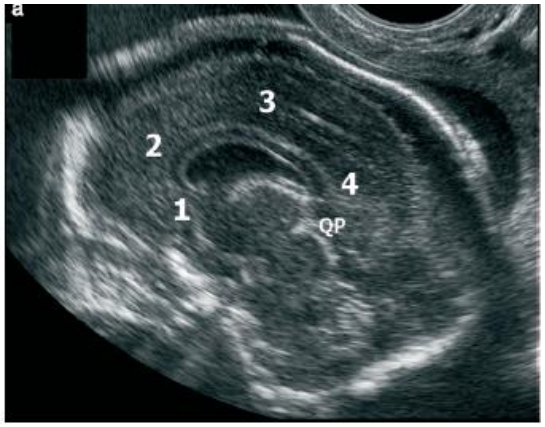
E' costituito da più di 190 milioni di assoni neuronali

Si forma tra la 8^ e la 17^ settimana di gestazione

Costituito da 4 parti

1. Rostro
2. Genu
3. Corpo
4. Splenio





Agenesia del corpo calloso (ACC)

La ACC è una tra le malformazioni congenita dell'encefalo più comunemente osservate.

Prevalenza nella popolazione generale: 1 – 7:1000.

Prevalenza tra le persone con disabilità intellettiva: 2 – 3%.

Può essere:

- Completa
- Parziale (ipogenesia o disgenesia)

ACC

Isolata

- Circa 1/3 dei casi
- Prognosi: 75-85% *outcome* positivo
- Osservate anomalie sostanza bianca intraemisferica, corteccia fronto-insulare e del giro del cingolo

Sindromica

- Fino all'80% dei casi presentano anomalie encefaliche associate (malformazione di Chiari II, malformazione di Dandy-Walker, difetti del tubo neurale, disordini di migrazione neuronale, oloprosencefalia),
- Fino al 60% dei casi presentano altre malformazioni maggiori associate.

Volpe et al., 2009

- Prognosi: conseguente al quadro malformativo

ACC: cause

- Genetiche → Nessun gene causativo noto specifico per ACC

  Il 30 – 45% dei casi di ACC hanno una causa identificabile

- Infettive: TORCH, etc…

- Vascolari

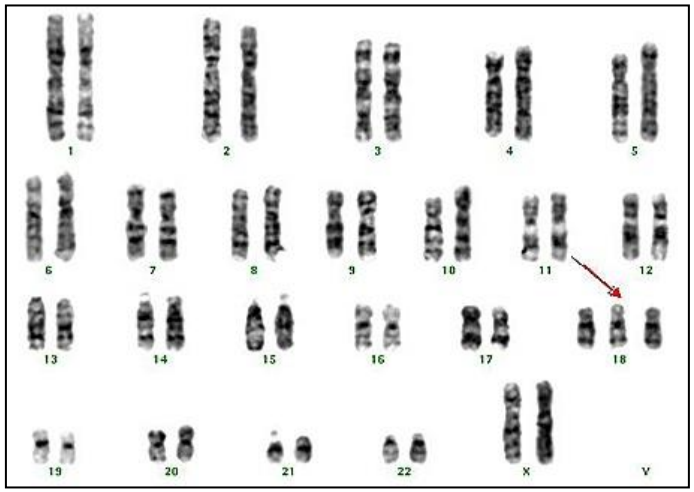
- Tossiche: alcool (ACC in 6,8% di casi con FAS), acido valproico, ipotiroidismo, etc…

Cause genetiche

Anomalie cromosomiche: 10% dei casi

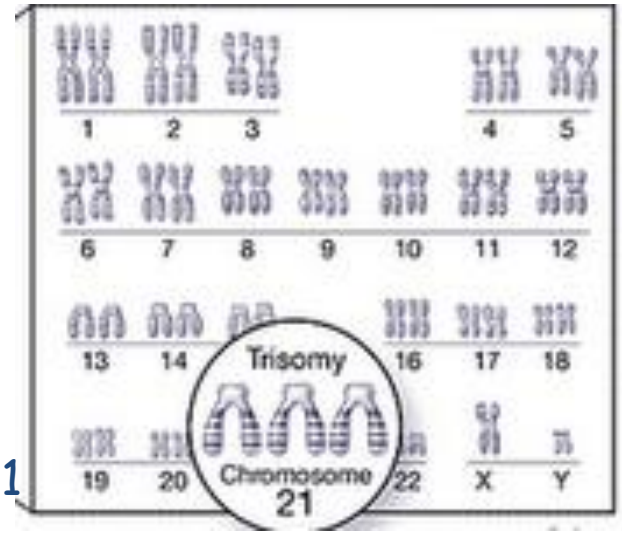
- Anomalie cromosomiche di numero

Trisomia 13



Trisomia 18

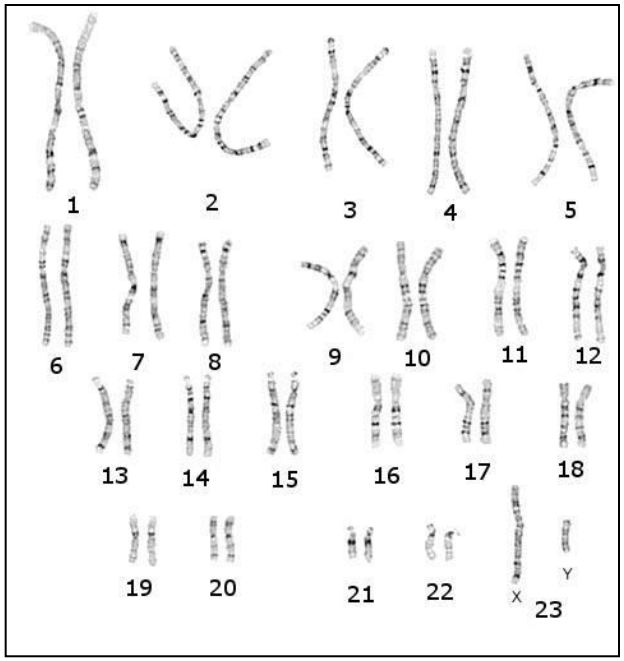
Trisomia 8 in mosaico,
Triploidia



Trisomia 21

- Anomalie cromosomiche di struttura

- **Chr 1**: del1q44, del1p31.3p32.2
- **Chr 2**: del2q14
- **Chr 4**: del4p16 (WHS)
- **Chr 5**: dup5p15.3p13.1, dup5p13.2
- **Chr 6**: del6q23, dup6p25
- **Chr 8**: dup8p21p23, del8q24.3

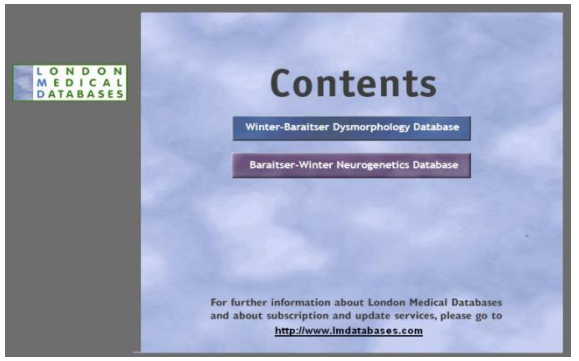


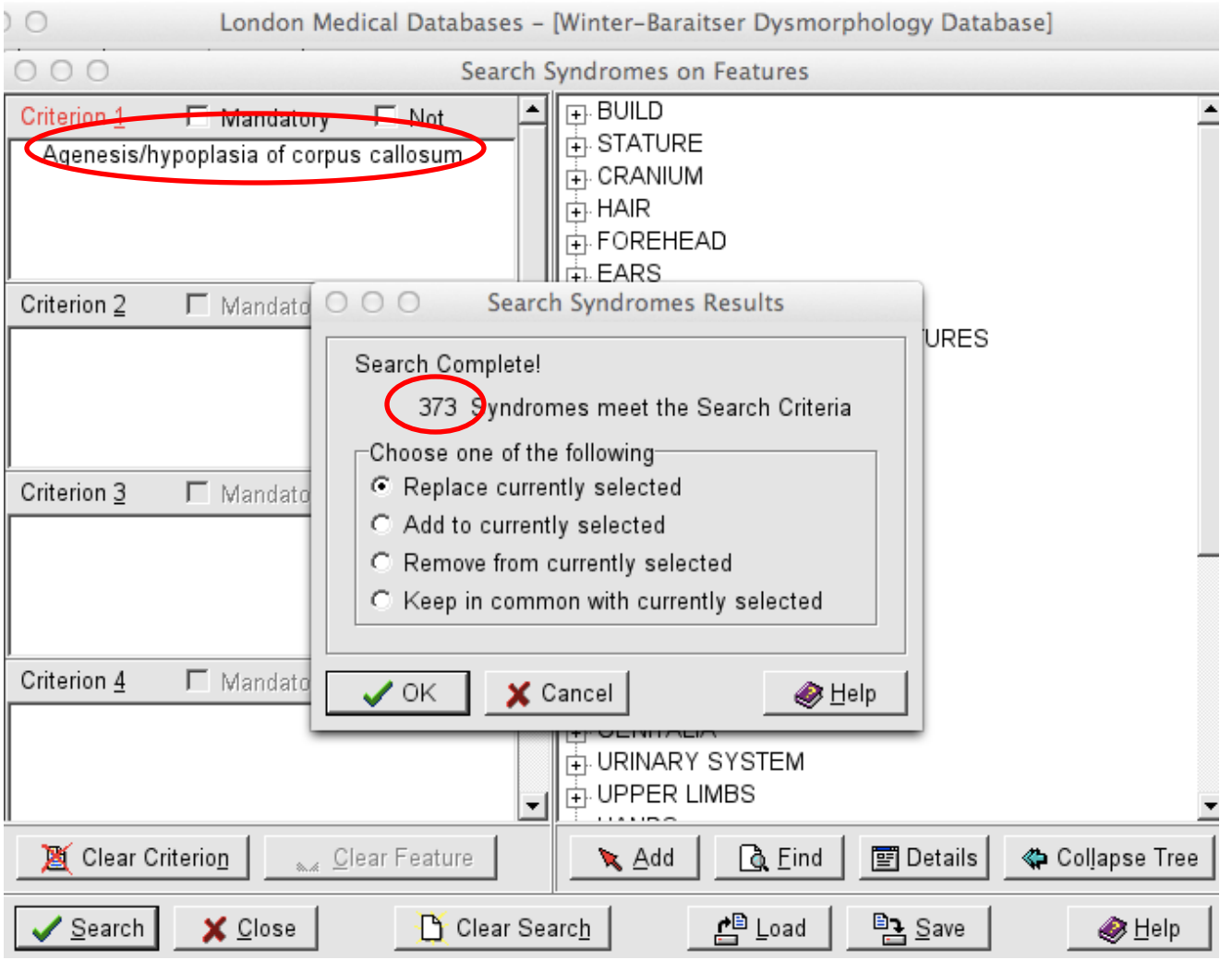
- **Chr 11**: dup11q23qter
- **Chr 13**: del13q13.32
- **Chr 14**: dup14q23q24
- **Chr 15**: del15q13
- **Chr 21**: del21q11q22.1
- **Chr 22**: del22q12
- **Chr X**: delXp22

Cause genetiche

Sindromi geniche: 20 - 35% dei casi

- AD (comprese forme sporadiche)
- AR
- XL
- Mitocondriali


LONDON MEDICAL DATABASES
Contents
Winter-Baraitser Dysmorphology Database
Baraitser-Winter Neurogenetics Database
For further information about London Medical Databases and about subscription and update services, please go to
http://www.lmdatabases.com


London Medical Databases - [Winter-Baraitser Dysmorphology Database]
Search Syndromes on Features
Criterion 1
Mandatory
Not
Agenesis/hypoplasia of corpus callosum
Criterion 2
Criterion 3
Criterion 4
BUILD
STATURE
CRANIUM
HAIR
FOREHEAD
EARS
URES
URINARY SYSTEM
UPPER LIMBS
Search Syndromes Results
Search Complete!
373 Syndromes meet the Search Criteria
Choose one of the following
Replace currently selected
Add to currently selected
Remove from currently selected
Keep in common with currently selected
OK
Cancel
Help
Clear Criterion
Clear Feature
Add
Find
Details
Collapse Tree
Search
Close
Clear Search
Load
Save
Help

Significato della diagnosi eziologica

- Prognosi
- Identificazione di trattamenti "medici e non"
- Prevenzione delle complicanze
- Non esecuzione di test diagnostici inutili
- Contatto con associazioni di genitori
- Consulenza genetica

Approccio metodologico al paziente con ACC

Difetto isolato ???

- Valutazione cardiologica con ECG ed ecocuore
- Ecoaddome completo
- Valutazione oculistica

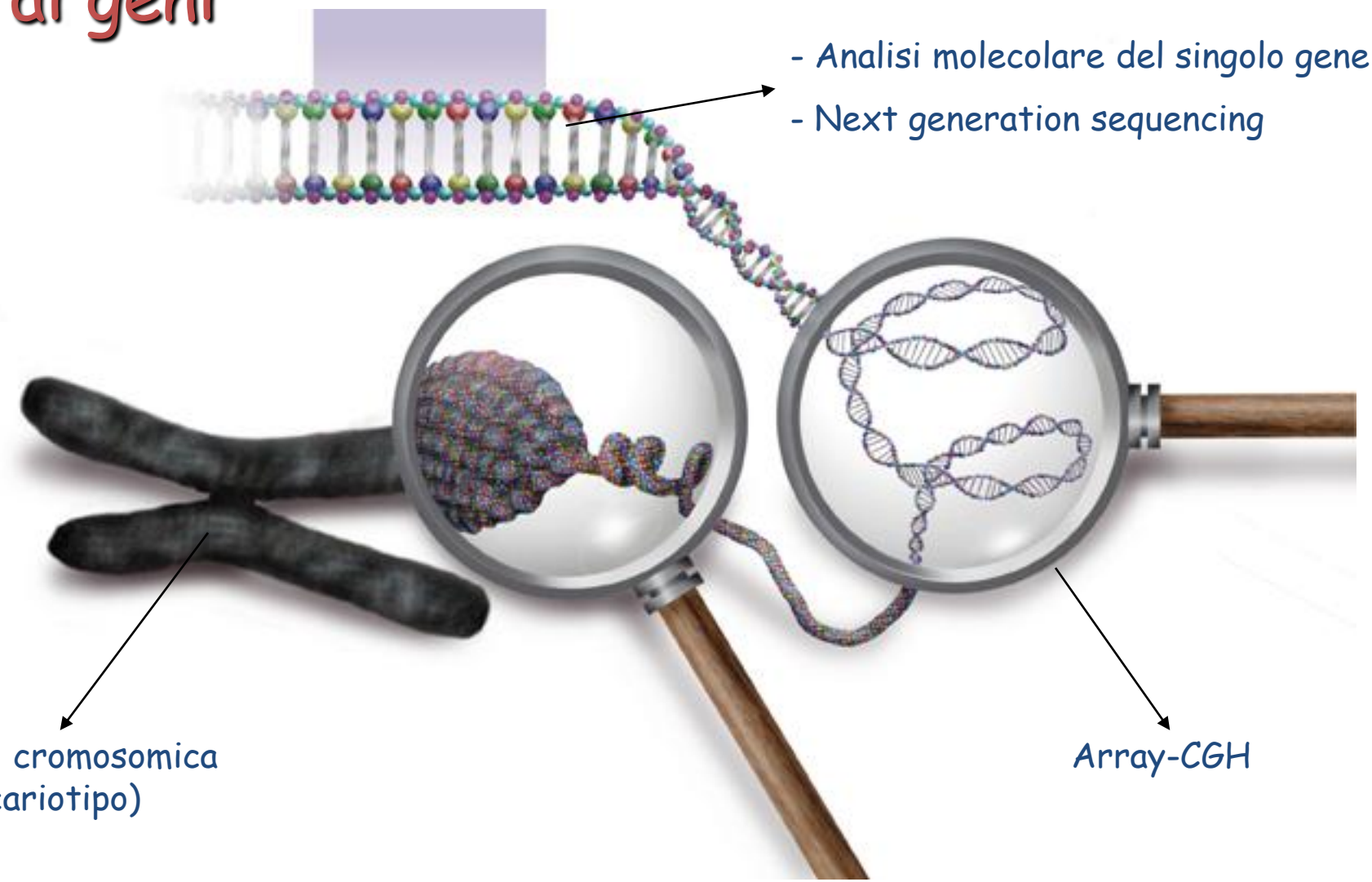
Condizione sindromica ???

Quadro plurisintomatico in cui sono variamente rappresentate le seguenti categorie di problemi:

- malformazioni maggiori
- malformazioni minori (dismorfismi)
- anomalie in eccesso o in difetto dell'accrescimento staturo-ponderale
- anomalie dello sviluppo (DD/ID)
- complicanze mediche

Indagini genetiche

Dai cromosomi ai geni



- Analisi molecolare del singolo gene
- Next generation sequencing

Analisi cromosomica (cariotipo)

Array-CGH

Indagini genetiche

ARTICLE

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

David T. Miller,[1,*] Margaret P. Adam,[2,3] Swaroop Aradhya,[4] Leslie G. Biesecker,[5] Arthur R. Brothman,[6] Nigel P. Carter,[7] Deanna M. Church,[8] John A. Crolla,[9] Evan E. Eichler,[10] Charles J. Epstein,[11] W. Andrew Faucett,[2] Lars Feuk,[12] Jan M. Friedman,[13] Ada Hamosh,[14] Laird Jackson,[15] Erin B. Kaminsky,[2] Klaas Kok,[16] Ian D. Krantz,[17] Robert M. Kuhn,[18] Charles Lee,[19] James M. Ostell,[8] Carla Rosenberg,[20] Stephen W. Scherer,[21] Nancy B. Spinner,[17] Dimitri J. Stavropoulos,[22] James H. Tepperberg,[23] Erik C. Thorland,[24] Joris R. Vermeesch,[25] Darrel J. Waggoner,[26] Michael S. Watson,[27] Christa Lese Martin,[2] and David H. Ledbetter[2,*]

Chromosomal microarray (CMA) is increasingly utilized for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), or multiple congenital anomalies (MCA). Performing CMA and G-banded karyotyping on every patient substantially increases the total cost of genetic testing. The International Standard Cytogenomic Array (ISCA) Consortium held two international workshops and conducted a literature review of 33 studies, including 21,698 patients tested by CMA. We provide an evidence-based summary of clinical cytogenetic testing comparing CMA to G-banded karyotyping with respect to technical advantages and limitations, diagnostic yield for various types of chromosomal aberrations, and issues that affect test interpretation. CMA offers a much higher diagnostic yield (15%–20%) for genetic testing of individuals with unexplained DD/ID, ASD, or MCA than a G-banded karyotype (~3%, excluding Down syndrome and other recognizable chromosomal syndromes), primarily because of its higher sensitivity for submicroscopic deletions and duplications. Truly balanced rearrangements and low-level mosaicism are generally not detectable by arrays, but these are relatively infrequent causes of abnormal phenotypes in this population (<1%). Available evidence strongly supports the use of CMA in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for patients with DD/ID, ASD, or MCA. G-banded karyotype analysis should be reserved for patients with obvious chromosomal syndromes (e.g., Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages.

The American Journal of Human Genetics *86*, 749–764, May 14, 2010

RESEARCH ARTICLE

Human Mutation

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High Frequency of Rare Copy Number Variants Affecting Functionally Related Genes in Patients with Structural Brain Malformations

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ABSTRACT: During the past years, significant advances have been made in our understanding of the development of the human brain, and much of this knowledge comes from genetic studies of disorders associated with abnormal brain development. We employed array-comparative genomic hybridization (CGH) to investigate copy number variants (CNVs) in a cohort of 169 patients with various structural brain malformations including lissencephaly, polymicrogyria, focal cortical dysplasia, and corpus callosum agenesis. The majority of the patients had intellectual disabilities (ID) and suffered from symptomatic epilepsy. We detected at least one rare CNV in 38 patients (22.5%). All genes located within the rare CNVs were subjected to enrichment analysis for specific Gene Ontology Terms or Kyoto Encyclopedia of Genes and Genomes pathways and to protein–protein network analysis. Based on these analyses, we propose that genes involved in "axonal transport," "cation transmembrane transporter activity," and the "c-Jun N-terminal kinase (JNK) cascade" play a significant role in the etiology of brain malformations. This is to the best of our knowledge the first systematic study of CNVs in patients with structural brain malformations and our data show that CNVs play an important role in the etiology of these malformations, either as direct causes or as genetic risk factors.

Hum Mutat 32:1427–1435, 2011. © 2011 Wiley Periodicals, Inc.

Table 1. Inherited Deletions and Duplications

Case	Chromosome band	Coordinates Hg18;Mb	Size Mb	CNV	Possible candidate genes[a]	Inheritance	Brain malformation/Phenotype
17807	2q36.3	228.1-228.3	0.24	Del	*SLC19A3*	Paternal	Focal cortical dysplasia, ID, epilepsy
5809	2q37.3	241.3-241.5	0.23	Dupl.	*KIF1A*	Maternal	Focal cortical dysplasia, ID, epilepsy
5842	3p22.3	36.8-37.0	0.29	Dupl.	*EPM2AIP*	Maternal	Focal cortical dysplasia, ID, epilepsy
5307	3p25.3	9.9-10.4	0.46	Dupl.	*Many*	Paternal	Hypoplasia of corpus callosum, ID, epilepsy
6657	3p26.1-2	3.9-4.8	0.96	Dupl.	*ITPR1*	Maternal	Hemimegalencephaly, corical dysplasia, polymicrogyria, partial corpus callosum agenesis, ID, epilepsy
6004	5p13.1-14.1	29.5-30.8	1.35	Dupl.		Paternal	Focal cortical dysplasia, pachygyria, ID, epilepsy
20732	5p12	12.9-13.2	0.29	Dupl.		Maternal	Microcephaly, ID
5349	5q12.3	65.5-65.9	0.43	Dupl.		Paternal	Nodular heterotopias, hypoplasia of corpus callosum, ID, epilepsy
5832	6p24.3	8.5-8.7	0.19	Del		Maternal	Focal cortical dysplasia, ID, epilepsy
20673	6p24.3	10.5-10.8	0.29	Del	*TFAP2A*	Maternal	Cerebellar hypoplasia, ID, epilepsy
22943	7p21.1	17.2-18.0	0.8	Dupl.	*AHR, SNX13*	Paternal	Corpus callosum agenesis, ID, epilepsy
22245	9p24.2	2.1-3.4	1.06	Dupl.	*SMARCA2, VLDLR*	Maternal	Pachygyria, ID, epilepsy
23779	9p21.2	27.2-27.4	0.2	Dupl.	*TEK, MOBKL2B*	Maternal	Dandy Walker malformation, ID
17500	10p15.3	1.1-1.6	0.55	Dupl.	*ADARB2*	Maternal	Dandy Walker, vermian hypoplasia, ID
22748	10q23.31	92.1-92.6	0.56	Dupl.	*HTR7*	Paternal	Focal cortical dysplasia, ID, epilepsy
6970	15q25.2	81.1-81.5	0.35	Del	*HOMER2*	Paternal	Hypoplasia of corpus callosum, delayed myelination, ID, epilepsy
18986	16p13.11	15.4-16.3	0.9	Dupl.	*NDE1*	Paternal	Focal cortical dysplasia, microcephaly, ID
6509	17p13.13	2.31-2.63	0.32	Dupl.	*PAFAH1B*	Not paternal	Focal cortical dysplasia, epilepsy
6107	17p12	11.9-12.1	0.18	Dupl.	*MAP2K*	Maternal	Corpus callosum agenesis, ID, epilepsy
6107	17p12	12.8-13.1	0.31	Dupl.	*RICH2, ELAC2*	Maternal	Corpus callosum agenesis, ID, epilepsy
5812	17q12	*31.4-33.7*	*2.29*	Dupl.	*LHX1, HNF1B*	Maternal	Focal cortical dysplasia, ID, epilepsy
6498	17q12	*33.0-33.4*	*0.44*	Dupl.	*HNF1B*	Maternal	Focal cortical dysplasia, ID, epilepsy
21003	18q23	73.1-73.8	0.67	Dupl.	*GALR*	Maternal	Microcephaly, ID, epilepsy
5809	22q13.32-3	*47.5-48.0*	*0.5*	Dupl.	*MAPK8IP2*	Maternal	Focal cortical dysplasia, ID, epilepsy
19958	Xp22.33	4.9-5.3	0.4	Dupl.		Maternal	Pachygyria, ID, epilepsy
19958	Xp22.33	3.9-4.2	0.3	Dupl.		Maternal	Pachygyria, ID, epilepsy
5809	Xp22.31	7.5-8.1	0.67	Dupl.	*PNPLA4*	Maternal	Focal cortical dysplasia, ID, epilepsy
17671	Xq21.31	85.1-85.7	0.61	Dupl.	*DACH2, CHM*	Maternal	Focal cortical dysplasia, ID
22392	Xq21.33	93.1-93.3	0.21	Dupl.		Maternal	Holoprosencephaly, ID, epilepsy
22392	Xq21.33	93.6-94.2	0.66	Dupl.		Maternal	Holoprosencephaly, ID, epilepsy

[a]Genes previously implicated in brain function and disease, or genes where either their expression pattern or known function suggest a role in brain development.
ID: intellectual disabilities.

Table 2. De novo Deletions and Duplications

Case	Chromosome band	Coordinates Hg18;Mb	Size Mb	Possible candidate genes[b]	CNV	Brain malformation/Phenotype
23376	1p36.32-23	4.95-15.3	10.3	*CLSTN1, KIF1B*	Del.	Corpus callosum agenesis, ID, epilepsy
17652	1q43-4	240.0-243.2	3.2	*AKT3, ZNF238*	Del.	Corpus callosum agenesis, microcephaly, ID, epilepsy
21835	2p25.3	0.42-3.0[a]	2.97	*MYT1L, TPO, SNTG2*	Del.	Focal cortical dysplasia, ID
21835	2p25.3	3.0-3.5[a]	0.45	*TSSC1*	Del.	Focal cortical dysplasia, ID
6223	2q22.3	144.7-145.3	0.6	*ZEB2*	Del.	Mowat Wilson Syndrome
17926	9q13-q21.3	70.2-74.98	4.78	*APBA1*	Del.	Corpus callosum agenesis, microcephaly, ID
17926	9q31.1-33.1	107.4-118.2	10.8	*FCMD, SLC31A2, SLC31A1, AMBP*	Dupl.	Corpus callosum agenesis, microcephaly, ID
20196	12p	p arm		*Many*	Mos.	Megalencephaly, ID, epilepsy
21753	12p	p arm		*Many*	Mos.	Megalencephaly, ID, epilepsy
22392	16p13.13	10.1-12.6	2.46	*Many*	Dupl.	Holoprosencephaly, ID, epilepsy
20375	17p13.3-2	1-3.4	3.39	*YWHAE, PAFAH1B*	Del.	Lissencephaly, ID, epilepsy
5538	17p13.3-2	2.3-3.7	1.34	*PAFAH1B*	Del.	Lissencephaly, ID, epilepsy
23510	17p13.3	2.3-3.5	1.1	*PAFAH1B*	Del.	Pachygyria, ID, epilepsy
6789	17p13.3	2.5-2.6	0.14	*PAFAH1B*	Del.	Lissencephaly, ID, epilepsy
21835	19q13.42	58.8-63.7	4.92	*TSEN34, NLRP12, TNNI3, CDC42EP5*	Dupl.	Focal cortical dysplasia, ID
19673	22q11	17.4-20.0	2.64	*CRKL*	Del.	Polymicrogyria, ID
7146	22q13.2-3	40.9-49.6	8.65	*MAPK8IP2*	Del.	Hypoplasia of corpus callosum, ID, epilepsy

[a] These two CNVs are separated by 1,6Mb in HG17.
[b] Genes previously implicated in brain function and disease, or genes where either their expression pattern or known function suggest a role in brain development.
ID: intellectual disabilities; Mos: mosaic.

ARTICLE

Mapping of Deletion and Translocation Breakpoints in 1q44 Implicates the Serine/Threonine Kinase AKT3 in Postnatal Microcephaly and Agenesis of the Corpus Callosum

Elena Boland, Jill Clayton-Smith, Victoria G. Woo, Shane McKee, Forbes D. C. Manson, Livija Medne, Elaine Zackai, Eric A. Swanson, David Fitzpatrick, Kathleen J. Millen, Elliott H. Sherr, William B. Dobyns, and Graeme C. M. Black

The American Journal of Human Genetics Volume 81 August 2007

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Neonatal Detection of 5p13.2 Duplication and Delineation of the Phenotype

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A newborn boy with broad forehead, mild microretrognathia, large hands and feet, arachnodactyly and a cortical thumb also had left renal agenesis, dysgenesis of corpus callosum with psychomotor delay. After oligonucleotide array comparative genomic hybridization (array-CGH) analysis, we detected a 900 kb duplication in cytoband 5p13.2, apperently a first clinical description. © 2012 Wiley Periodicals, Inc.

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

A Homozygous Deletion of 8q24.3 Including the *NIBP* Gene Associated With Severe Developmental Delay, Dysgenesis of the Corpus Callosum, and Dysmorphic Facial Features

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Eur J Pediatr (2010) 169:463–468
DOI 10.1007/s00431-009-1057-2

ORIGINAL PAPER

A novel 1p31.3p32.2 deletion involving the *NFIA* gene detected by array CGH in a patient with macrocephaly and hypoplasia of the corpus callosum

Udo Koehler · Elke Holinski-Feder · Birgit Ertl-Wagner · Juergen Kunz · Arpad von Moers · Hubertus von Voss · Chayim Schell-Apacik

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Toriello-Carey Syndrome With a 6Mb Interstitial Deletion at 22q12 Detected by Array CGH

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Toriello–Carey syndrome is a rare multiple congenital anomaly syndrome comprising agenesis of the corpus callosum, telecanthus, short palpebral fissures, abnormal ears, Pierre Robin sequence, and cardiac anomaly. Autosomal recessive inheritance

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2011. Toriello–Carey syndrome with a 6Mb

Array-CGH → Negativo

373 sindromi con ACC

(diagnosi in 20 – 35% dei casi)

Anamnesi – Esame obiettivo

+

Malformazioni maggiori

+

Complicanze mediche

} **"Maniglie diagnostiche"**

"Maniglie diagnostiche"

↓

Strumenti informatici di ausilio diagnostico (LMD, Possum, OMIM), motori di ricerca (PubMed)

↓

Diagnosi differenziale

↓

Sospetto diagnostico

Esami genetici "specifici" per sindromi monogeniche

Disabilità intellettiva (ID)

- 254 sindromi con ACC e ID -

Anomalie associate	Sindrome
ID + macrocefalia	•Sindrome FG (XL, geni MED12, FLNA e CASK) •Sindrome acro-callosa (AR, gene GLI3) •Sindrome cranio-cerebello-cardiaca (AR) •Sindrome di Sotos (AD, gene NSD1)
ID + microcefalia	•Sindrome di Joubert (AR, eterogeneità genetica) •Sindromi CDG (AR, eterogeneità genetica) •Sindrome di Rubinstein Taybi (AD, geni CPB e EP300) •Sindrome di Seckel (AR, geni ATR e PCNT) •Sindrome di Coffin-Siris (AR) •Sindrome di Leigh (AR,XL,mit., geni SURF1, TYKY e MTATP6)
ID + retinopatia	•Sindrome Aicardi (XLD) •Sindrome di Joubert (AR, eterogeneità genetica) •Sindromi CDG (AR, eterogeneità genetica) •Sindrome di Leigh (AR,XL,mit., geni SURF1, TYKY e MTATP6) •Sindrome di Rubinstein Taybi (AD, geni CPB e EP300) •MEB (AR, geni POMGnT1 e POMT2) •Adrenoleucodistrofia (XL, gene ABCD1; neonatale: AR, gene PXR1PEX3) •Mucolipidosi (AR, eterogeneità genetica) •Sindrome cranio-cerebello-cardiaca (AR)

*

Anomalie associate	Sindrome
ID + ipoacusia neurosensoriale	•Sindrome FG (XL, geni MED12, FLNA e CASK) •Sindrome acro-callosa (AR, gene GLI3) •Adrenoleucodistrofia neonatale (AR, gene PXR1PEX3)
ID + cardiopatia congenita	•Sindrome di Sotos (AD, gene NSD1) •Sindrome di Leigh (AR,XL,mit., geni SURF1, TYKY e MTATP6) •Sindrome FG (XL, geni MED12, FLNA e CASK) Sindrome G/BBB di Opitz (Eterogeneità genetica: del22q, gene Xp22 MID1) •Sindrome di Coffin-Siris (AR) •Sindrome acro-callosa (AR, gene GLI3)
ID + contratture articolari	•Sindrome di Marden-Walker (AR) •Sindromi CDG (AR, eterogeneità genetica) •Sindrome cerebro-oculo-facio-scheletrica (COFS)(AR, geni CSB, XPD-G/GS e ERC) •Sindrome FG (XL, geni MED12, FLNA e CASK)
ID + displasia corticale	•Sindrome Aicardi (XLD) •MEB (AR, geni POMGnT1 e POMT2) •Sindrome di Seckel (AR, geni ATR e PCNT) •Sindrome di Marshall-Smith (ereditarietà incerta) •Sindrome di Galloway-Mowat (AR) •XLAG (XL, gene ARX)

Anomalie associate	Sindrome
ID + miopatia	•MEB (AR, geni POMGnT1 e POMT2) •Sindrome di Marden-Walker (AR) •Sindrome di Leigh (AR,XL,mit., geni SURF1, TYKY e MTATP6) •Sindromi CDG (AR, eterogeneità genetica) •Adrenoleucodistrofia neonatale (AR, gene PXR1PEX3)
ID + nefropatia congenita	•Sindrome di Sotos (AD, gene NSD1) •Sindrome di Fryns (AR) •Sindrome oro-facio-digitale (OFD) tipo 1 (XLD, gene CXORF5) •Sindrome di Marden-Walker (AR) •Sindrome di Rubinstein Taybi (AD, geni CPB e EP300) Sindrome di Marshall-Smith (ereditarietà incerta)
ID + palatoschisi	•Sindrome Aicardi (XLD) •Sindrome ATR16 (Sporadica, microdelezione 16p) e ATRX (XL, gene XPN) •Sindrome OFD tipo 1 (XLD, gene CXORF5) •Sindrome di Marden-Walker (AR) •Sindrome G/BBB di Opitz (Eterogeneità genetica: microdelezione 22q, mutazione gene Xp22 MID1) •Sindrome di Baller-Gerold (AR, gene RECQL4) •Sindrome di Coffin-Siris (AR) •Sindrome di Seckel (AR, geni ATR e PCNT) •Sindrome di Rubinstein Taybi (AD, geni CPB e EP300)

Indagini genetiche

Rapid Review

Exome sequencing: a transformative technology

Andrew B Singleton

Lancet Neurol 2011; 10: 942–46

Summary

Background Much basic research into disease mechanisms has made use of genetic findings to

REPORT

VPS35 Mutations in Parkinson Disease

Carles Vilariño-Güell,[1,15,*] Christian Wider,[2,15] Owen A. Ross,[3] Justus C. Dachsel,[3] Jennifer M. Kachergus,[3] Sarah J. Lincoln,[3] Alexandra I. Soto-Ortolaza,[3] Stephanie A. Cobb,[3] Greggory J. Wilhoite,[3] Justin A. Bacon,[3] Bahareh Behrouz,[3] Heather L. Melrose,[3] Emna Hentati,[3] Andreas Puschmann,[3,4] Daniel M. Evans,[1] Elizabeth Conibear,[1] Wyeth W. Wasserman,[1] Jan O. Aasly,[5] Pierre R. Burkhard,[6] Ruth Djaldetti,[7] Joseph Ghika,[2] Faycal Hentati,[8] Anna Krygowska-Wajs,[9] Tim Lynch,[10,11] Eldad Melamed,[7] Alex Rajput,[12] Ali H. Rajput,[12] Alessandra Solida,[2] Ruey-Meei Wu,[13] Ryan J. Uitti,[14] Zbigniew K. Wszolek,[14] Francois Vingerhoets,[2] and Matthew J. Farrer[1,3]

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REPORT

A Mutation in *VPS35*, Encoding a Subunit of the Retromer Complex, Causes Late-Onset Parkinson Disease

Alexander Zimprich,[1,14,*] Anna Benet-Pagès,[2,14] Walter Struhal,[3,14] Elisabeth Graf,[2,14] Sebastian H. Eck,[2] Marc N. Offman,[4] Dietrich Haubenberger,[1] Sabine Spielberger,[5] Eva C. Schulte,[2,6] Peter Lichtner,[2] Shaila C. Rossle,[4] Norman Klopp,[7] Elisabeth Wolf,[5] Klaus Seppi,[5] Walter Pirker,[1] Stefan Presslauer,[8] Brit Mollenhauer,[9] Regina Katzenschlager,[10] Thomas Foki,[1] Christoph Hotzy,[1] Eva Reinthaler,[1] Ashot Harutyunyan,[11] Robert Kralovics,[11] Annette Peters,[7] Fritz Zimprich,[1] Thomas Brücke,[8] Werner Poewe,[5] Eduard Auff,[1] Claudia Trenkwalder,[9,12] Burkhard Rost,[4] Gerhard Ransmayr,[3] Juliane Winkelmann,[2,6,13] Thomas Meitinger,[2,13] and Tim M. Strom[2,13,*]

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nature genetics

Heterozygous missense mutations in *SMARCA2* cause Nicolaides-Baraitser syndrome

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Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome

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A Mosaic Activating Mutation in *AKT1* Associated with the Proteus Syndrome

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Rischio genetico

"Potrà verificarsi di nuovo alle prossime gravidanze ?"

ACC

Isolata → Le forme isolate sono soprattutto casi sporadici (mutazione *de novo* di un gene dominante, ipotesi multifattoriale), rischio di ricorrenza ragionevolmente intorno al 5%

Descritta ereditarietà AD, AR, XL: rischio di ricorrenza conseguente al pattern di trasmisisone

Sindromica (cromosomica, genica) → Nelle forme sindromiche il rischio di ricorrenza è conseguente alla natura (ereditario o *de novo*) ed al tipo (cromosomico o genico) di difetto genetico: *counselling* specifico per la condizione diagnosticata

Nelle forme sindromiche sporadiche non definite nosologicamente: rischio di ricorrenza intorno al 5 – 10%