


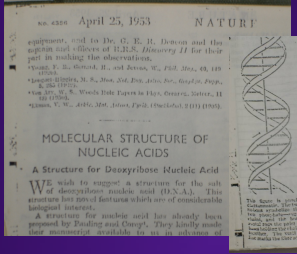
VANDERBILT UNIVERSITY
MEDICAL CENTER

Genetic Factors Contributing to Disabilities

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October 17, 2012





April 25, 1953

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribonucleic Acid

WE wish to propose a structure for the salt of deoxyribonucleic acid (D.N.A.). This structure has two of the main characteristics of considerable biological interest.

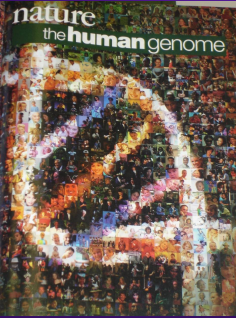
A structure for nucleic acid has already been proposed by Pauling and Corey. They largely made their reasoning available to us in a preliminary report.

Francis Crick James Watson Maurice Wilkins Rosalind Franklin

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material..."

"We have also been stimulated by a knowledge of ... the unpublished experimental results and ideas of Dr. M.H.F. Wilkins, Dr R.E. Franklin and their coworkers at King's College, London."

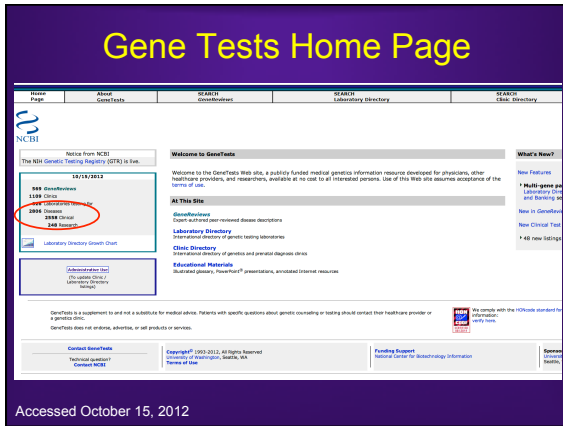
Human Genome Published February, 2001

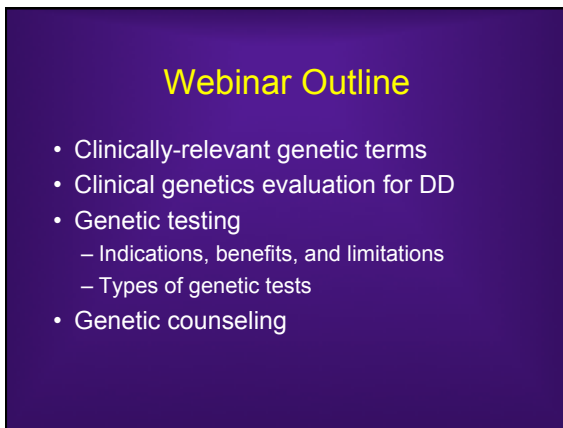


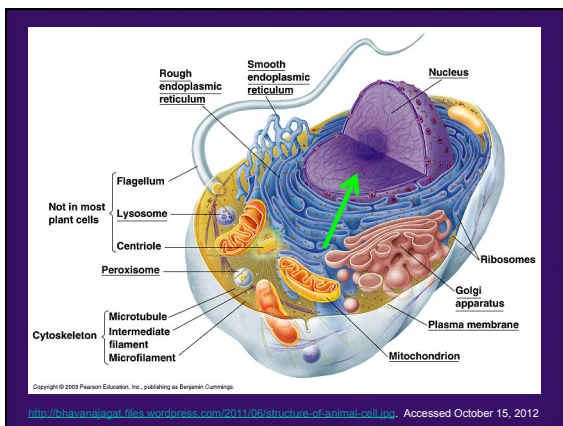
nature
the human genome

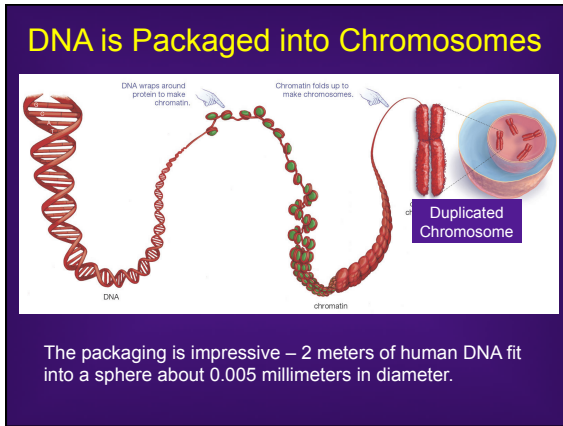
Science
THE HUMAN GENOME

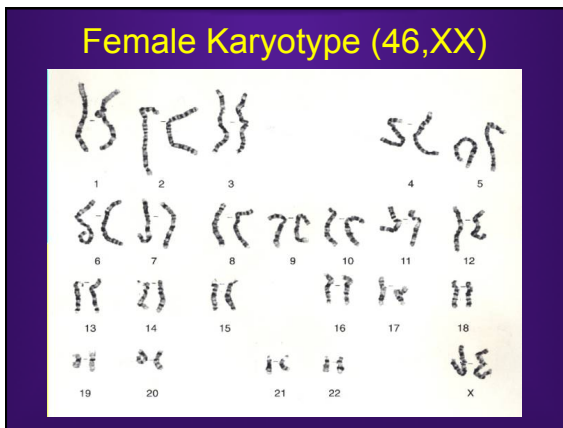
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

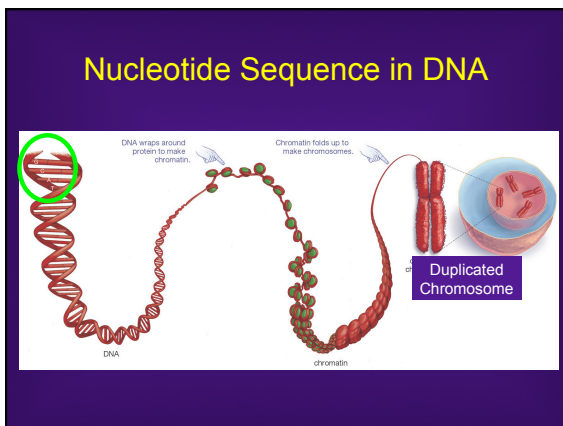












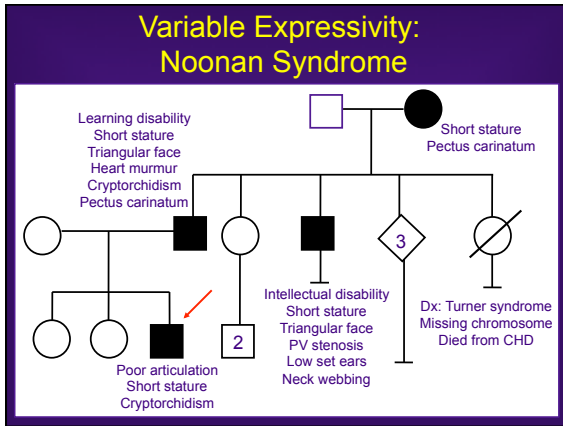
Mutations and Alleles

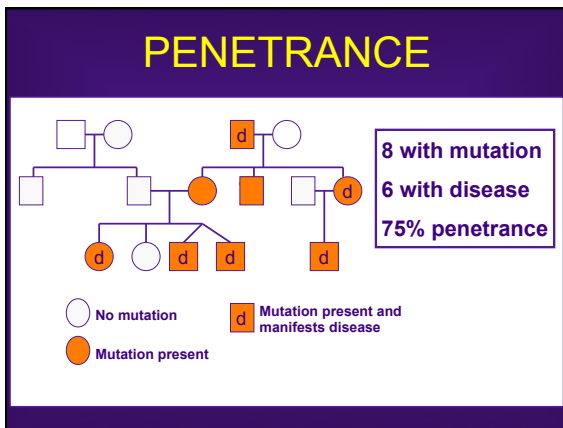
- Mutation
 - Any change in DNA sequence
 - Not necessarily pathologic
- Allele
 - Specific DNA sequence in a gene in an individual
 - Allele 1: A at position 14
 - Allele 2: C at position 14
- Polymorphism
 - Allele present in $\geq 1\%$
- Rare Variant
 - Allele present in $<1\%$

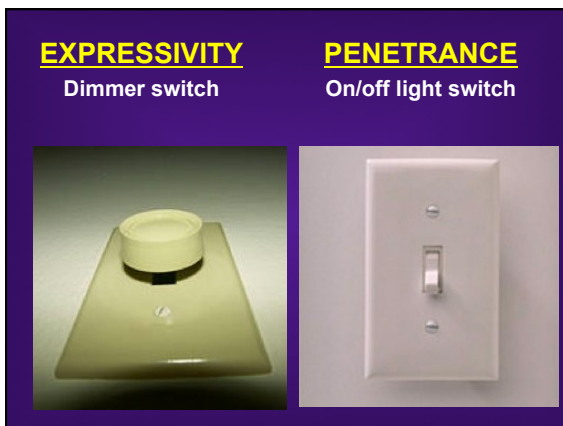
Genotype and Phenotype

- Genotype
 - Specific alleles in an individual
- Phenotype
 - Traits or characteristics of an individual
 - Product of genotype and environment
- Genotype – phenotype correlation

<p><u>EXPRESSIVITY</u></p> <p>The extent to which a genetic defect is expressed. The trait may vary from mild to severe, but never completely unexpressed in those with the genotype.</p>	<p><u>PENETRANCE</u></p> <p>Fraction of individuals with a genotype known to cause disease who have any signs/symptoms of the disease.</p>
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Webinar Outline

- Clinically-relevant genetic terms
- Clinical genetics evaluation for DD
- Genetic testing
 - Indications, benefits, and limitations
 - Types of genetic tests
- Genetic counseling

Selected Indications for Referral to Genetics

- Determine genetic etiology to developmental concern (autism, ID, malformation, GDD)
- Previous child with neurodevelopmental disability or congenital malformations
- Family history of hereditary condition, including CA
- History of pregnancy loss or infertility
- Abnormal newborn screen for inborn metabolic disease
- Abnormal prenatal testing (US, maternal screen)
- Possible teratogenic effect

Clinical Genetics Approach

- Use medical history, family history, physical examination, and prior laboratory results to determine appropriate diagnostic evaluation.
- Screen for potential comorbidities (such as hypothyroidism in DS) or malformations
- Discuss goals of care with family to determine if genetic testing is desired.
- Confirm that patient is receiving appropriate medical interventions.

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Selected Benefits of Genetic Testing

- Treatment and management
- Prognosis (range of outcomes)
- Recurrence risk and family planning
- Potential enrollment in research study
- Potential participation in specific support group
- Empowerment

Limitations of Genetic Testing

- Normal results do NOT rule out possibility of genetic etiology
- Making diagnosis of a genetic cause for DD does not *typically* guide the use of specific medication or interventions (eg. therapy)
- Financial, emotional & time costs

High-Resolution Karyotype

- Microscopic evaluation of chromosomes
- Resolution: 4-5 Mb
- Identifies trisomies, translocations, inversions, large deletions or duplications
- Example conditions
 - Trisomy 21
 - Turner syndrome
 - Partial monosomies
 - Partial trisomies

Fluorescence *In-Situ* Hybridization (FISH)

- Probe for specific area of single chromosome (locus)
- Resolution: 40,000 – 250,00 bp
- Detects deletion or duplication at locus
- Clinical conditions:
 - Velo-cardio-facial syndrome (22q11 deletion)
 - Williams syndrome (7q11.23 deletion)
 - Smith-Magenis syndrome (17p11.2)

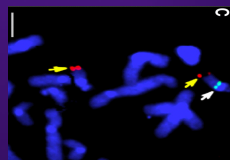
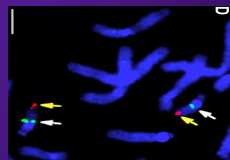
FISH for 22q11 Deletion

Red signal: Identifies chromosome 22

Green signal: Identifies 22q11 region

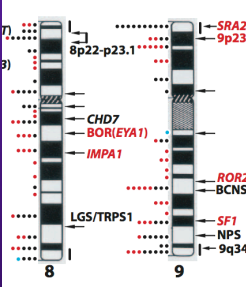
2 red signals to identify both chromosome 22s

Only 1 green signal; therefore, deletion at 22q11



Chromosomal Microarray Analysis

- Detects submicroscopic deletions & duplications
- Example array
 - 400,000 oligonucleotides
 - Known syndrome regions
 - Subtelomere regions
 - Dispersed throughout genome
 - ≥4800 genes with exon by exon coverage
 - Complete mtDNA
- Diagnostic yield is about 8-12% for ASD and ID



<http://www.bcm.edu/cma/assets/CHIPMAPV6.pdf>

New Genetic Syndrome

- 9 year old boy
- ID with autistic features
- Dysmorphic facial features
- Affected mother and brother
- CMA: MeCP2 duplication
- New syndrome identified in 2005 based on CMA

Del Gaudio et al. *Genet Med* 2006;8:784

DNA Molecular Testing (Sanger Sequencing)

- Determine specific nucleotides in a particular gene or panel of genes
- Example: sequencing MeCP2 for Rett syndrome
- “Whole gene” sequencing vs. common mutations
- Possible results of testing include normal (including benign variant), abnormal and *variant of unknown significance*
- Variants of unknown significance frequently require testing of parents or other family members

Next-Generation Sequencing (NGS)

- NGS provides opportunity to sequence the entire exome or genome
- Millions of short fragments of DNA sequenced simultaneously (massively parallel sequencing)
- Advances in IT support essential to analyze enormous volume of data (gigabytes)
- Whole exome sequencing (WES) available on a clinical basis
- Cost, time, and counseling needs are current limitations for NGS

Biochemical Testing

- Metabolite testing (newborn screen, amino and organic acids, acylcarnitine profile)
- Large number of tests with relative low yield for most cases of developmental disability
- Pattern of abnormalities important
- Abnormal results rarely pathognomonic (diagnostic of a specific disease)
- Follow up or confirmatory analysis typically required (enzyme testing, DNA sequencing)
- (Used to follow many Pts with metabolic d/o)

Genetic Testing

Name	Test	Abnormalities Detected
Karyotype	Microscopic evaluation of all chromosomes Resolution: 4-5 Mb	Trisomies, large rearrangements, and inversions
Fluorescence <i>in situ</i> hybridization (FISH)	Single chromosome locus Resolution: Submicroscopic changes (40,000 – 250,000 bp)	Continuous gene deletions/duplications (copy number variants)
Chromosomal microarray analysis (CMA)	≥400K oligonucleotides or millions of single nucleotide polymorphisms (SNP) (<u>depends on version</u>) Resolution: 30 Kb	Oligonucleotide or SNP duplications/deletions (copy number variants)
Molecular testing (Sanger sequencing)	Sequencing of exons and exon/intron borders of specific gene(s)	Point mutations, frameshifts, small deletions, insertions, etc.
Biochemical testing	Metabolites associated with inborn metabolic disease, including newborn screening	Amino acids, organic acids, acylcarnitine profile, etc.

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Pre-test Genetic Counseling

- *Premise is that genetic testing is fundamentally different than other types of laboratory tests.*
- Provide risk assessment based on medical and family history (distinguish “genetic” from “hereditary”)
- Discuss patient’s and/or family’s priorities, values, beliefs, and goals
- Discuss benefits and limitations of performing genetic testing and not performing genetic testing
- Describe genetic testing options
- Describe logistics of genetic testing
- Discuss potential results of testing
- Provide psychosocial support with referrals, if indicated

Post-test Genetic Counseling

- Disclose genetic test results and prognosis
- Review expressivity and penetrance of condition
- Discuss treatment options for patient
- Review recurrence risk and reproduction options based on results of testing
- Provide psychosocial support with referrals, if indicated.
- Document information in counseling letter

Clinical Genetics References

- Gene Tests (www.geneclinics.org)
- Online Mendelian Inheritance in Man (OMIM) website
- Gorlin, Cohen, and Hennekam. *Syndromes of the Head and Neck*. Oxford, 2001.
- Cassidy SB and Allanson JE. *Management of Genetic Syndromes, Second Edition*. Wiley, 2005.

The screenshot shows the AUCD 2012 website for a pre-conference workshop. The header includes the AUCD logo and the slogan "Innovating Today Shaping Tomorrow" with the date "December 2-5, 2012" and location "Washington, DC". The main content area is titled "AUCD - Pre-Conference Workshop 7: Essential Clinical Genetics for LEND and UCEDD Programs". It lists the date and time as "Sunday, December 2, 2012 12:30 PM - 3:00 PM" and the location as "Columbia 10". A list of featured presenters includes Tyler Reimschisel, Robert W. Martin, Karen Edwards, John Moschler, and Jaerin Bodurha. A session description follows, explaining that the workshop will provide knowledge, skills, and attitudes for healthcare professionals to integrate genetics into the care of individuals with neurodevelopmental disabilities. A sidebar on the left contains navigation links for Home, Conference Invitation & Overview, Presentation Details, Presentation Accessibility, Registration, Hotel, Agenda & Program, Shipping to the Hotel, and Transportation. A URL and access date are provided at the bottom: "http://www.aucd.org/conference/detail/session_event_id=388&showday=1. Accessed October 16, 2012."

Questions?

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