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The information contained in this presentation is not intended as a substitute for professional medical advice, diagnosis or treatment.
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You Are One in a Million: Precision Medicine and the Future of Healthcare

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What is Precision Medicine?

- The concept of “[disease] prevention and treatment strategies that take individual variability into account.”

Francis Collins and Harold Varmus, NEJM 2015

Every Disease is Genetic

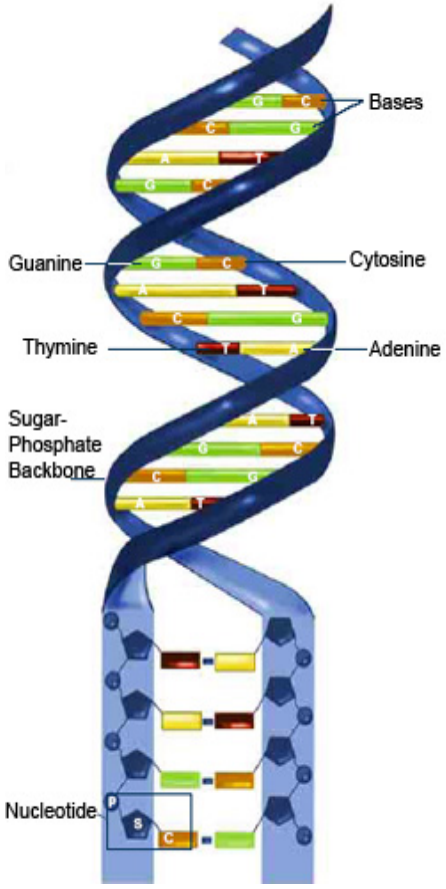
- “Monogenic” : caused by a mutation in one gene. Mutation in that single gene makes disease highly likely
- “Complex” : caused by mutations (variations) in several genes with subtle effects on their function that combine to set the stage for illness

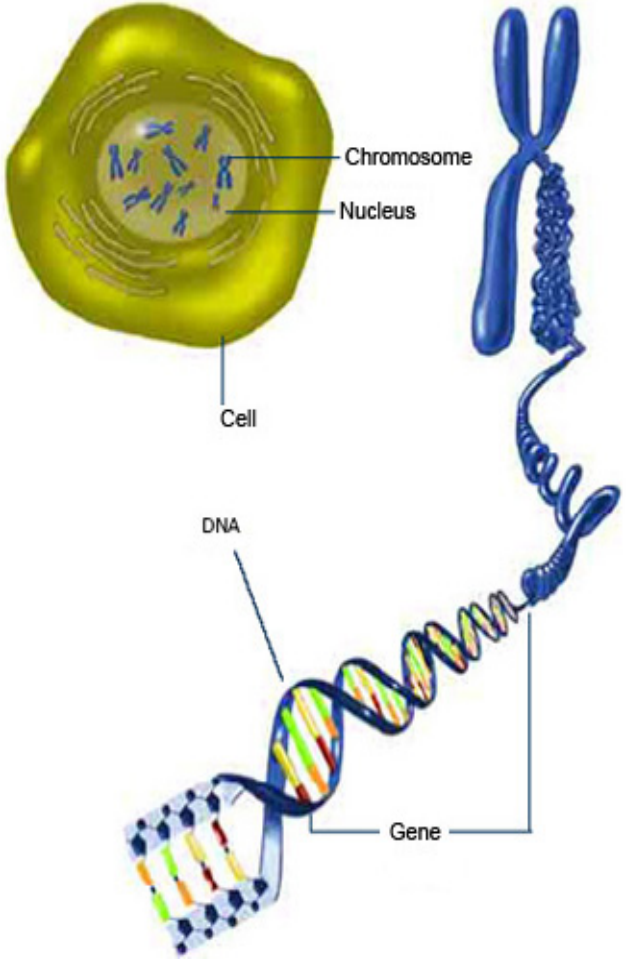
Monogenic Disorders

- Inherited
  - passed from parent(s) to child
  - may show “Mendelian” inheritance
  - Non-Mendelian (incomplete penetrance): requires mutation in one gene, but additional factors determine whether symptoms occur (ex: familial BRCA1 mutation has an 80% lifetime risk of breast cancer)

- Acquired (*de novo*) mutation
  - may occur *early* and affect all cells in an embryo
  - may occur early and only in egg or sperm (germline mosaic)
  - may occur later and affect only somatic cells (mosaic)

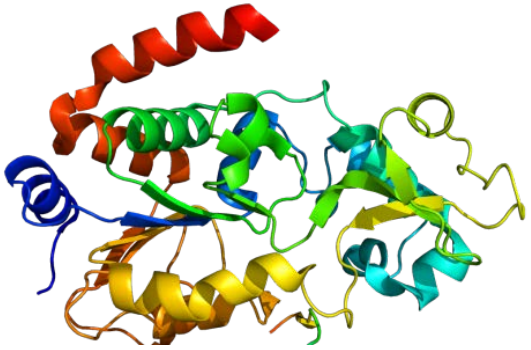
DNA encodes our genetic blueprint for proteins





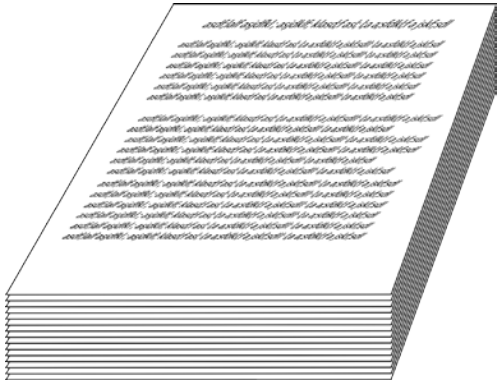
The genome:

Protein:

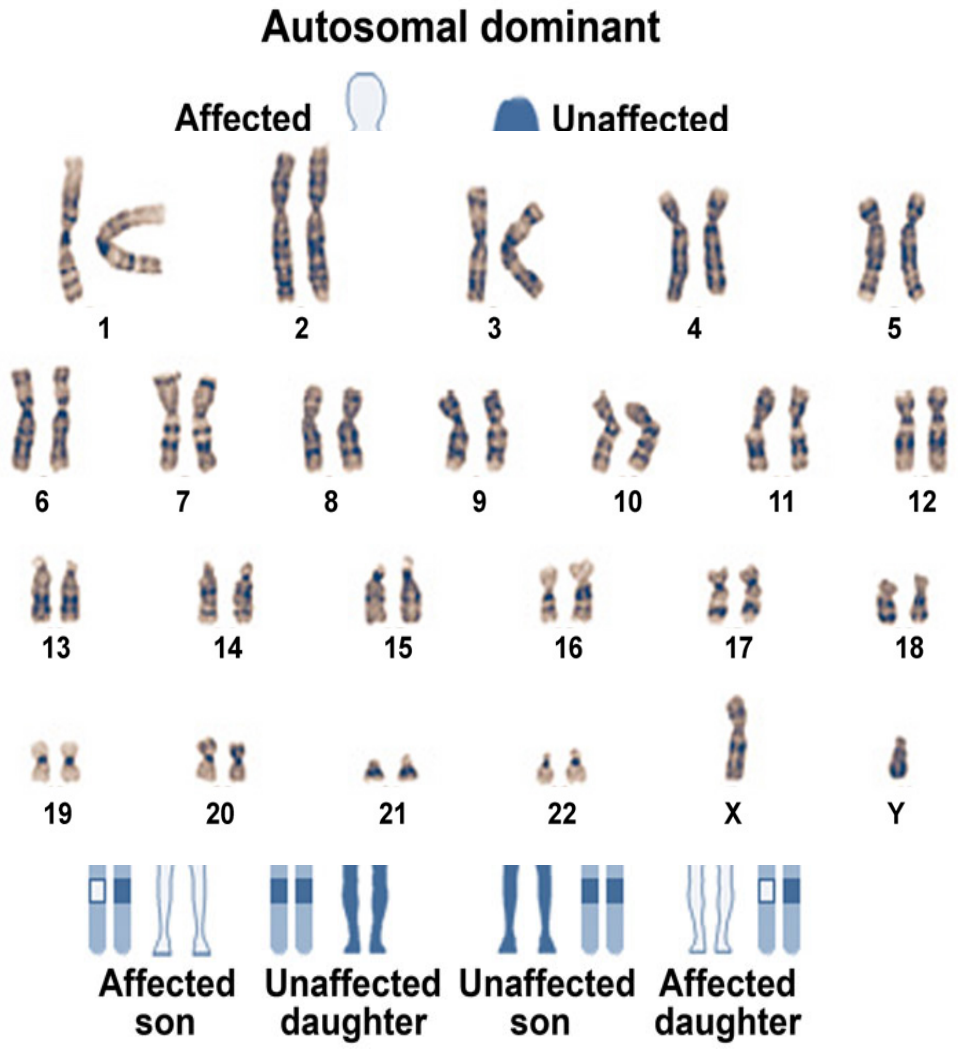


A gene (DNA):

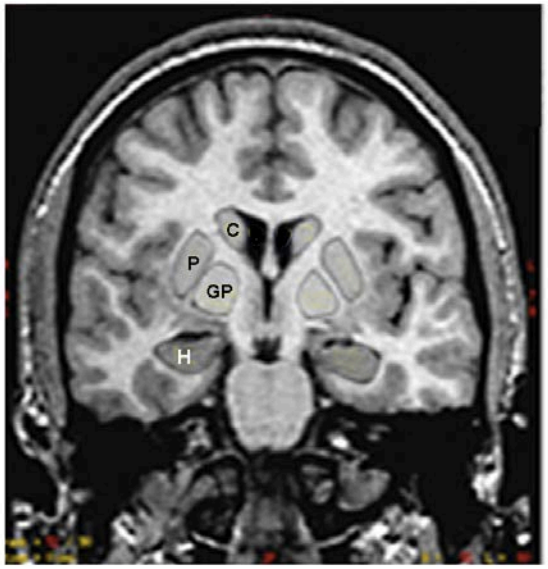
The copy (RNA)



Our Genes are ‘Dealt’ from a ‘Deck’ of 23 Chromosome Pairs

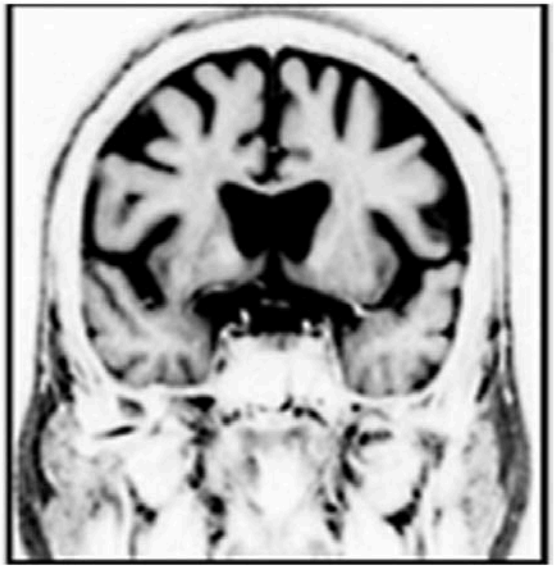


Huntington's Disease: Dominant mutation on Chromosome 4, Huntingtin gene

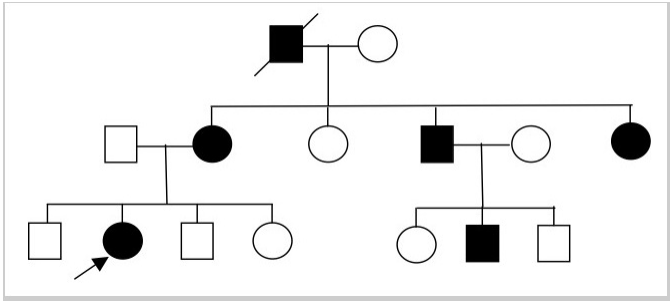


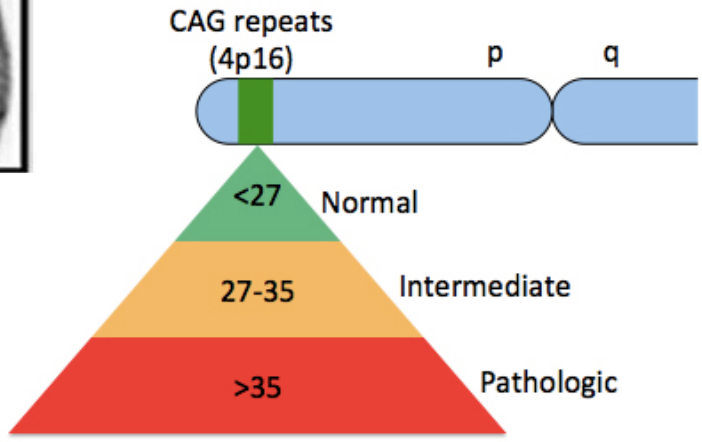
Normal

C=Caudate H=Hippocampus
P=Putamen
GP=Globus Pallidus



Advanced HD





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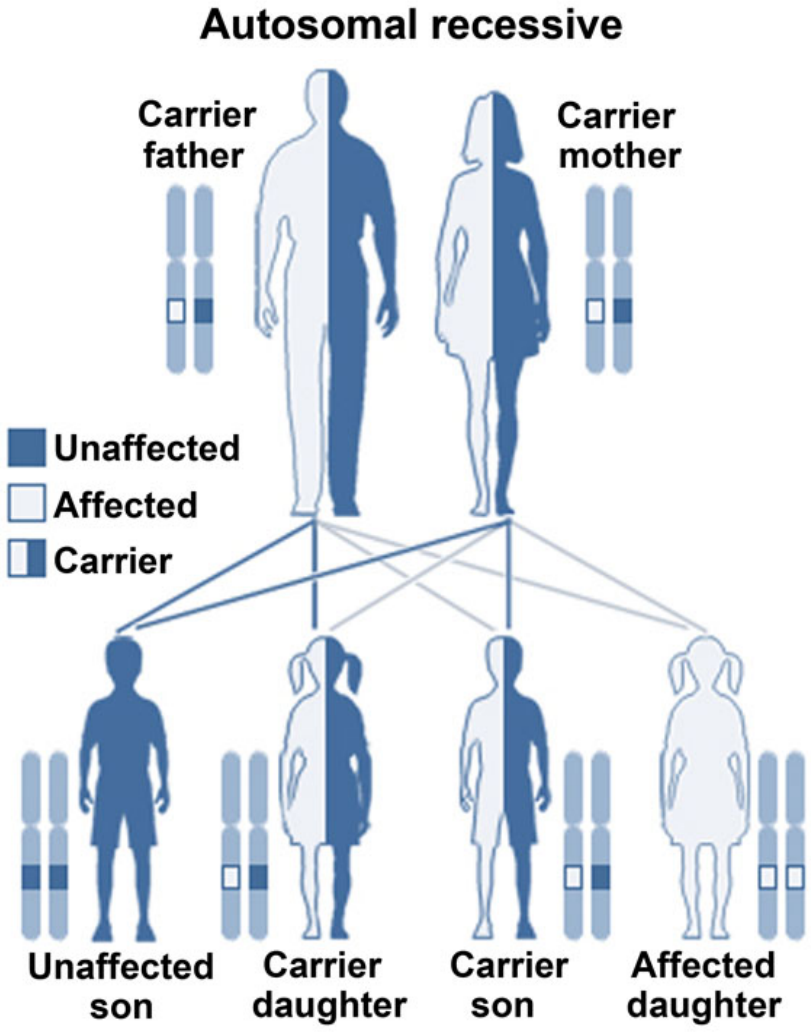
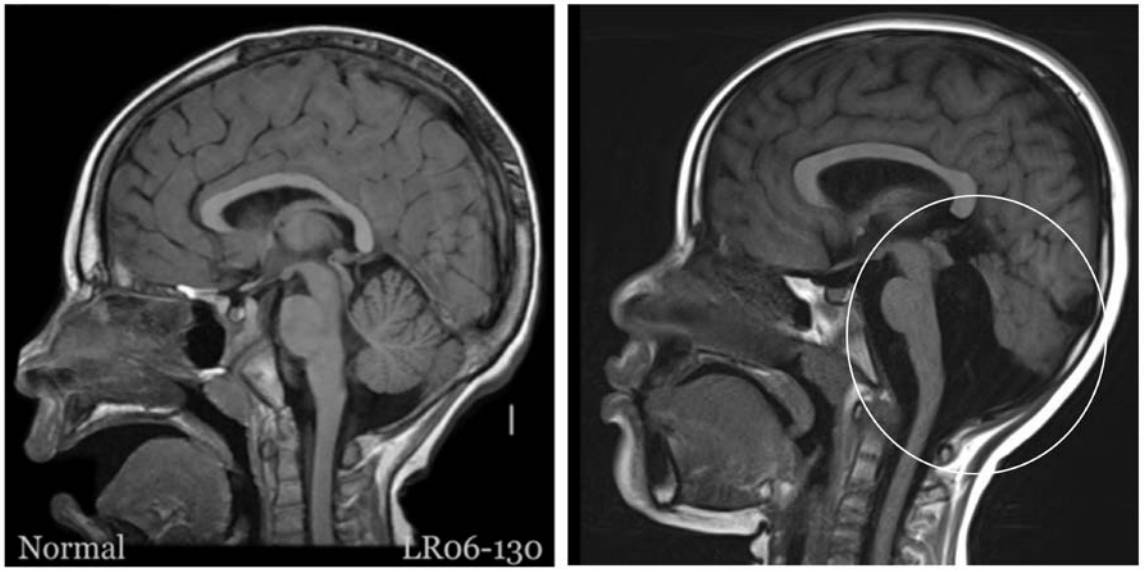
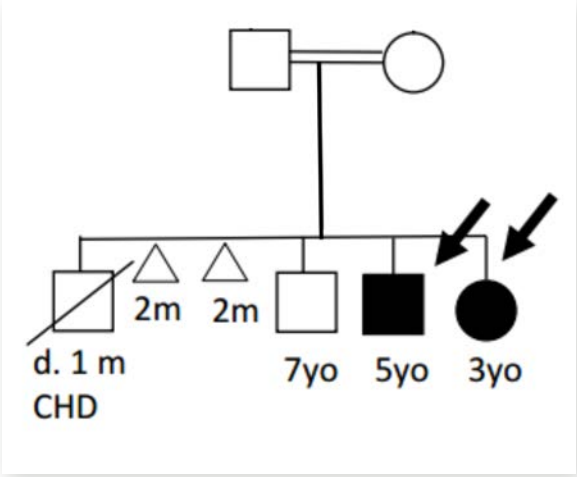
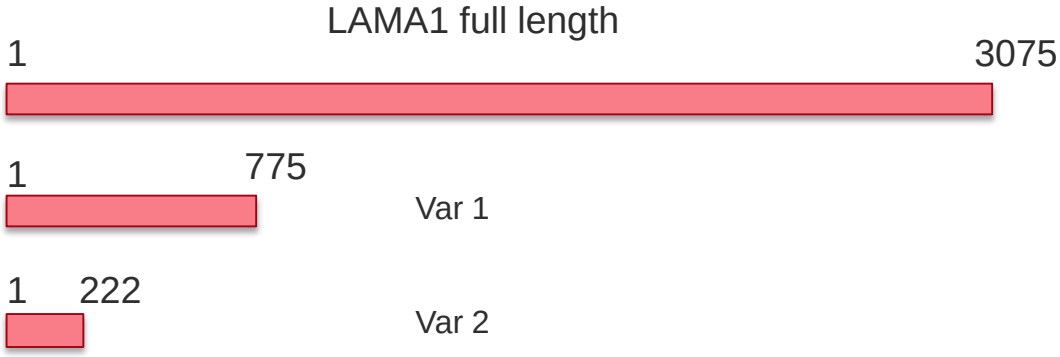


Cerebellar Ataxia: Recessive mutation on Chromosome 18, LAMA1 gene

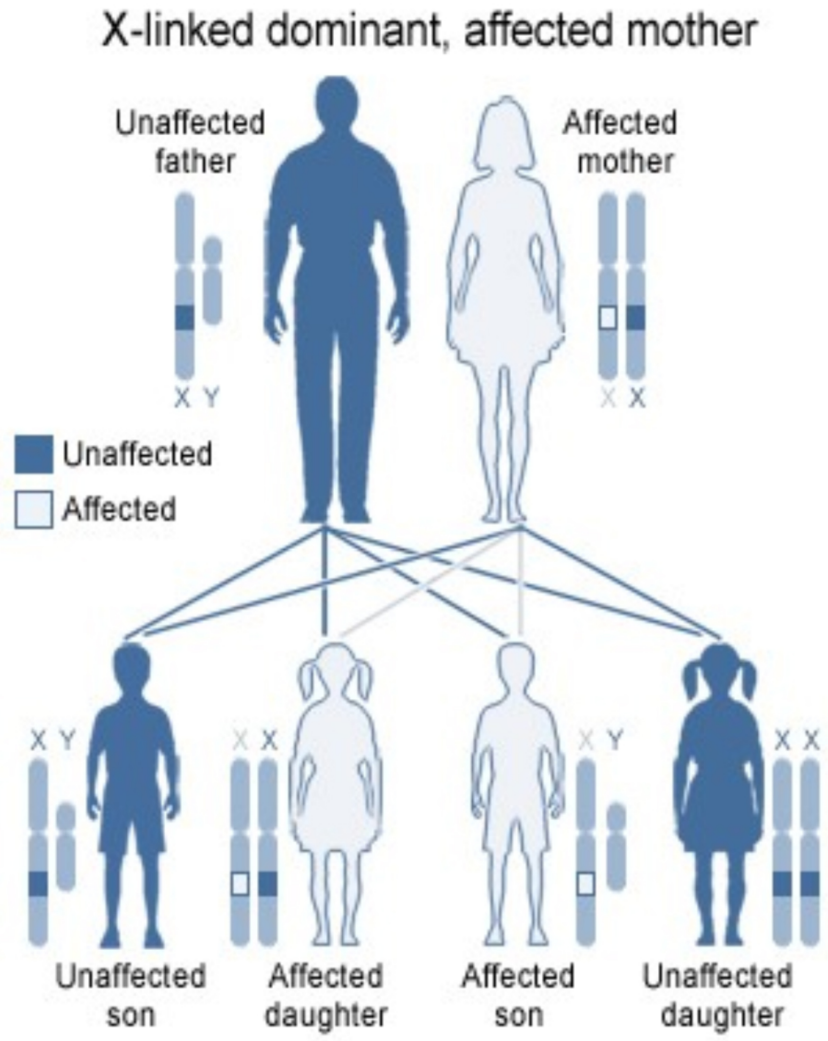




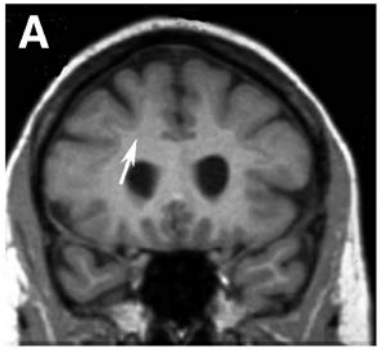


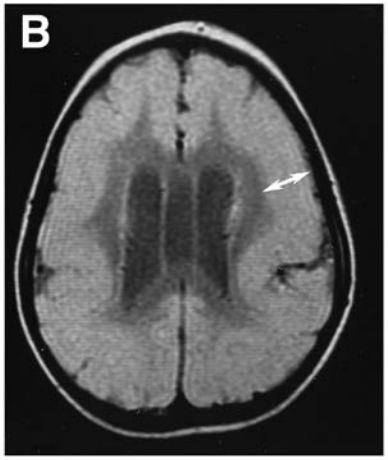
- Cerebellar ataxia,
  Developmental delay
  Retinal dystrophy

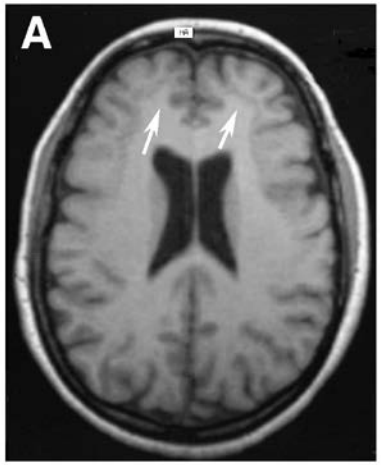
Our Genes are ‘Dealt’ from a ‘Deck’ of 23 Chromosome Pairs

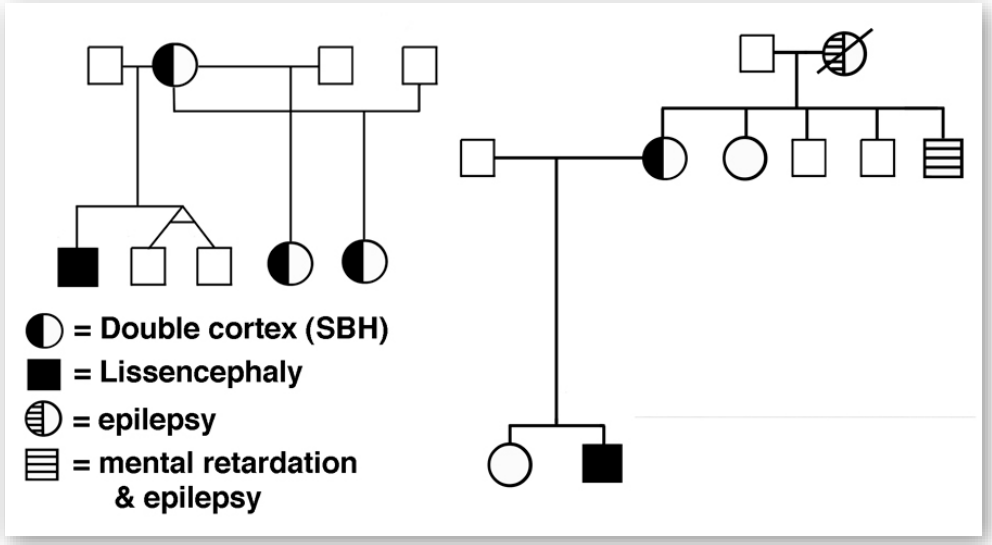


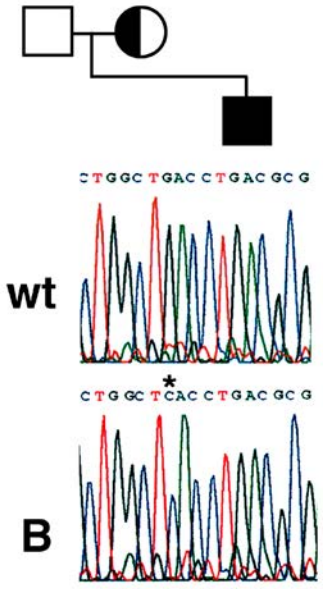
X-Linked Lissencephaly: X-Linked recessive mutation, Doublecortin gene



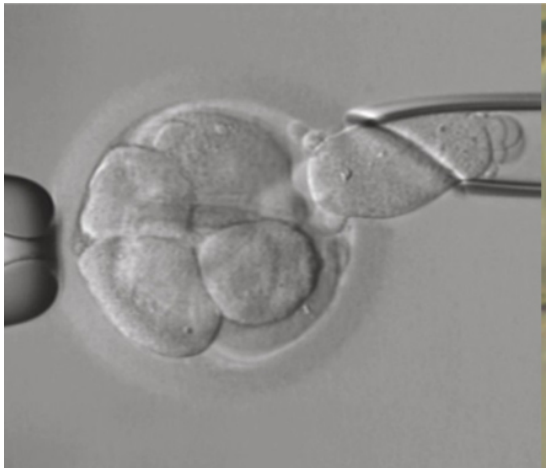


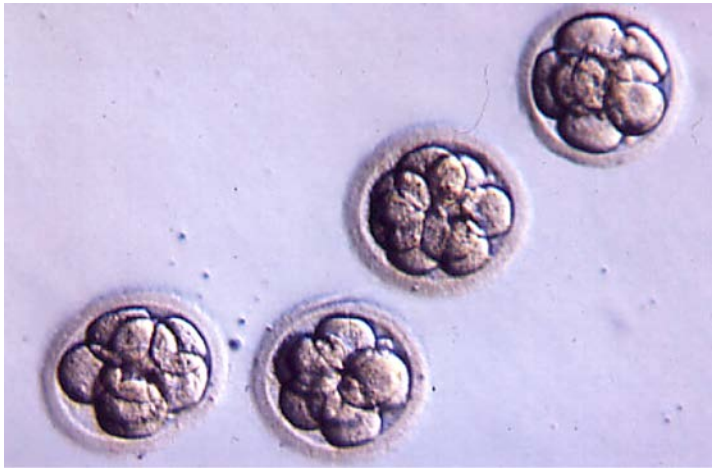






Preimplantation Diagnosis (PGD)





- Post IVF, remove one cell from a 3 to 5 day embryo, extract DNA and sequence for known mutation
- Exclude embryos with the mutation from implantation

Complex Genetic Disorders

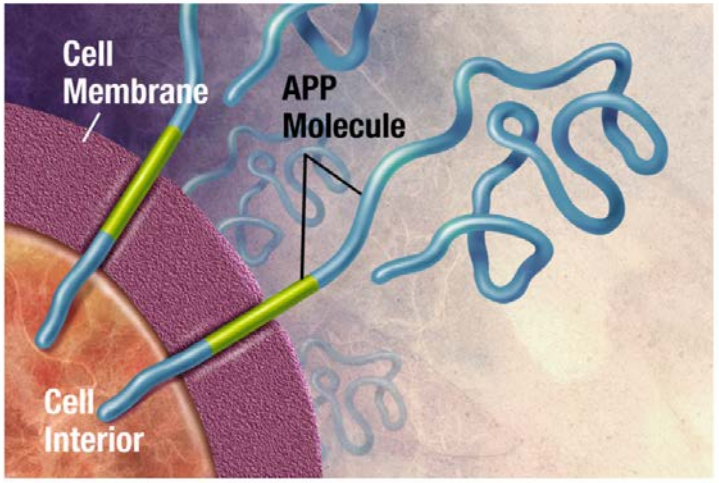
- Caused by variations in several genes with subtle effects on their function that combine to set the stage for illness

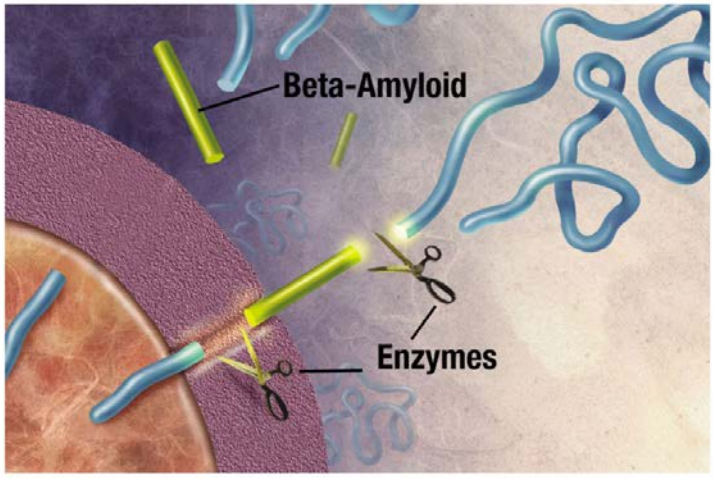
- Examples include:
  - Neural Tube Defects (Spina bifida)
  - Autism Spectrum Disorder (ASD)
  - Schizophrenia
  - Epilepsy
  - Parkinson's Disease
  - Alzheimer's Disease

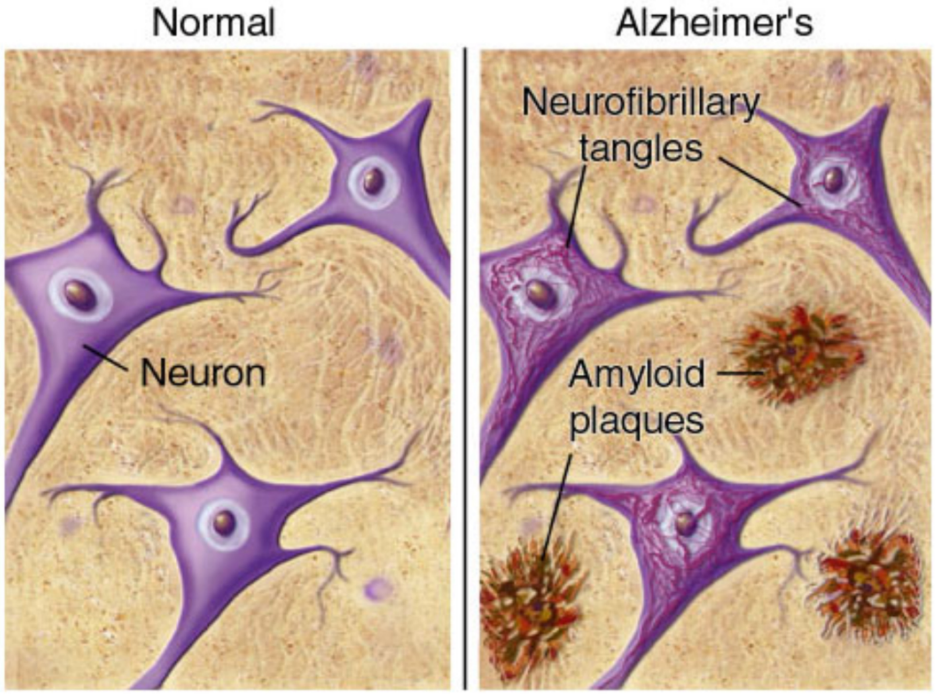
Alzheimer's Disease (AD)

- Uncommon before age 65, risk doubles every 5 years thereafter
- Rates reach 42% of adults older than 84 years
- Third leading cause of death in elders behind heart disease and cancer
- In 2006 an estimated 27 million afflicted by AD, expected to quadruple by 2050 (48 million in 2015)
- Familial AD (13% of AD cases), at least 3 causative genes known: amyloid precursor protein (APP), presinilin 1 and 2 (PSEN1/2)

Alzheimer’s Disease (AD)





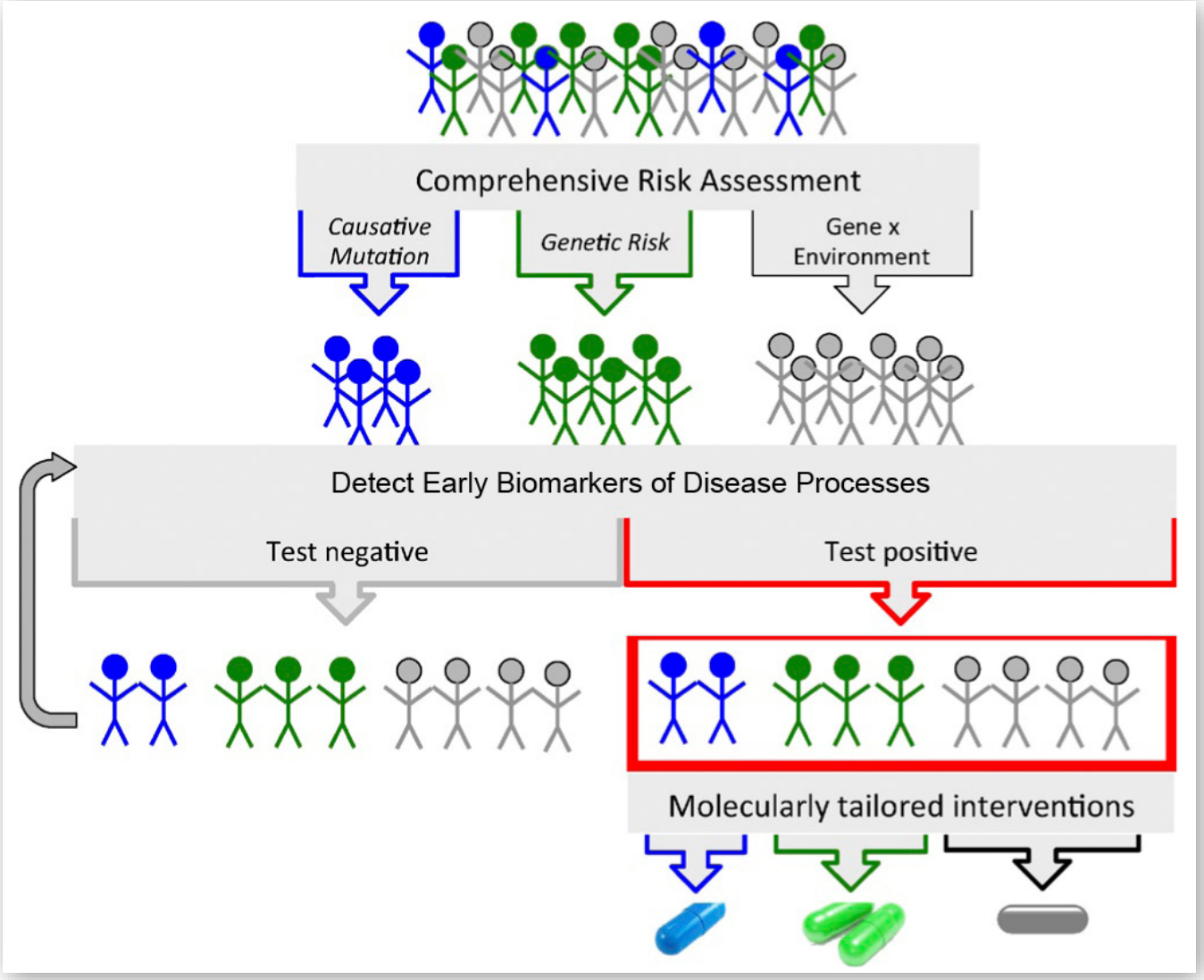


Alzheimer's Disease (AD)

- 85% of cases are complex, gene-environment determined
- Risk genes for AD identified through Genome-Wide Association Studies (GWAS)
- 19 different genes identified (so far) that increase the risk of developing AD
- Apolipoprotein E ε4 allele is the strongest.
  - -- APOEε4/ε4 genotype increases AD risk 15 times,
  - -- ε3/ε4 raises risk 3 times, while
  - -- ε2 may be protective against AD

What mix of these gene variations confer highest risk?
How can we prevent or slow the process?

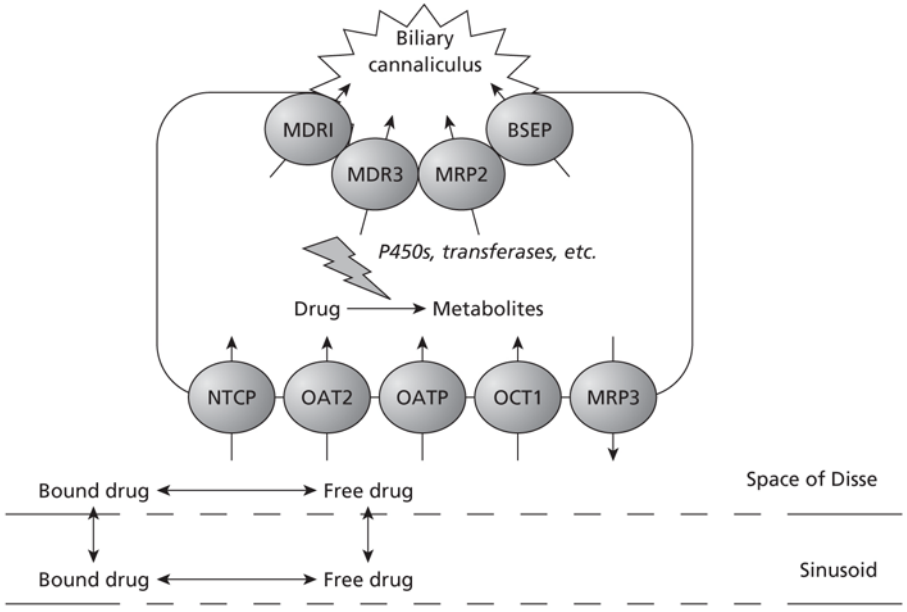
Precision Medicine for Neurological Disorders



Precision Medicine for All of Us: Pharmacogenomics

Genetic variants in liver enzymes and transport proteins influence how medications are metabolized in the liver

The liver is the drug clearance organ of the body regulating:
-- how much of a drug is absorbed from the GI tract
-- how long the drug will remain in the system
-- liver enzymes break down or metabolize drugs into intermediate chemicals that may be “active” (either therapeutic or cause side effects)



A Few Medications Handled by the Liver

Medication class	Examples	Medication class	Examples
Antibiotics	sulfonamides (e.g. Bactrim)	Statins	Simvastatin
	ciclosporin		Prevastatin
	erythromycin	Antiplatelet agents	clopidogrel (Plavix)
	rifampin		aspirin
	isoniazid	Anticoagulants	warfarin (Coumadin)
Anticonvulsants	phenytoin (Dilantin)		apixaban (Eliquis)
	phenobarbital	Antihypertensives	hydralazine
	lamotrigine		methyldopa
	carbamazepine (Tegretol)		atenolol
	diazepam	Chemotherapy	5-FU
	valproate (Depakote)		vincristine (oncovin)
Antidepressants	imipramine (Elavil)		
	fluoxetine (Prozac)		
	other SSRIs (Zoloft, Paxil)		
	St Johns wort		

Everyone will take a medication sometime

- Some variants in genes expressed in liver are known to impact drug transport, metabolism or degradation.
- Recently 10,000 individuals were screened for known gene variants related to 5 medications and 90% of study participants had 1 or more “actionable” variants.
- Everyone of us is likely to have one or more gene variants that if known would indicate a particular drug should be avoided or that a higher or lower dose should be used.
- Genome sequencing for common variants of medication metabolism can guide choice of most effective medicine with fewest side effects for the individual.
- There are many more gene variants to be found that are important for different ethnic backgrounds.

Precision Medicine: NOT Just Genomics

NYC Consortium

All of Us Research Program

What is the *All of Us* Research Program?

"A longitudinal research effort to enroll one million U.S. participants to prevent and treat disease based on individual differences in lifestyle, environment and genetics."

All of Us RESEARCH PROGRAM | The Precision Medicine Initiative

Columbia University Medical Center | NYC Health + Hospitals | Harlem | Weill Cornell Medicine | NewYork-Presbyterian

Objectives for the *All of Us* Research Program

The Program aims **to build a participant cohort** for exploration of biological, clinical, social, and environmental determinants of health and disease.

The Program will **collect and curate health-related data and biosamples** from one million or more individuals who reflect the diversity in the United States.

Data and biosamples will be made available **for research use** and there will be strict procedures and permissions in place to access it.

Specifics about the *All of Us* Research Program

Timeline and targets:

- Launched July 2017
- We estimate it will take up to five years to reach 1 million participants
- WCM has an overall enrollment goal of approximately 69,000

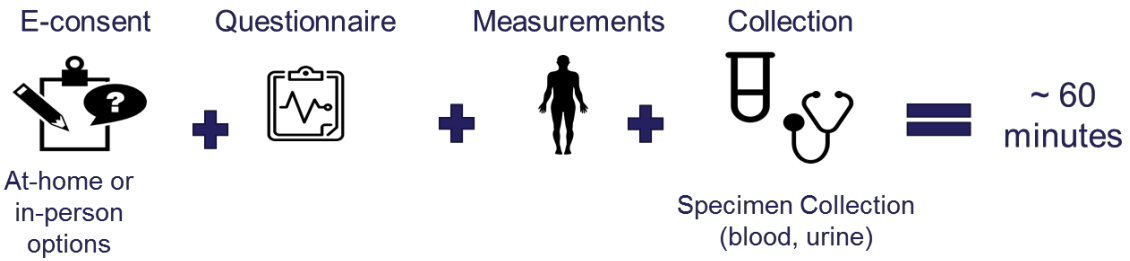
Data set collection includes:

- Health questionnaires (medical, lifestyle, and environmental)
- Physical measurements (blood pressure, height, weight, hip and waist ratios)
- Biospecimens (blood and urine)
- Electronic health record discrete data

Become One in a Million

Enrollment Steps:

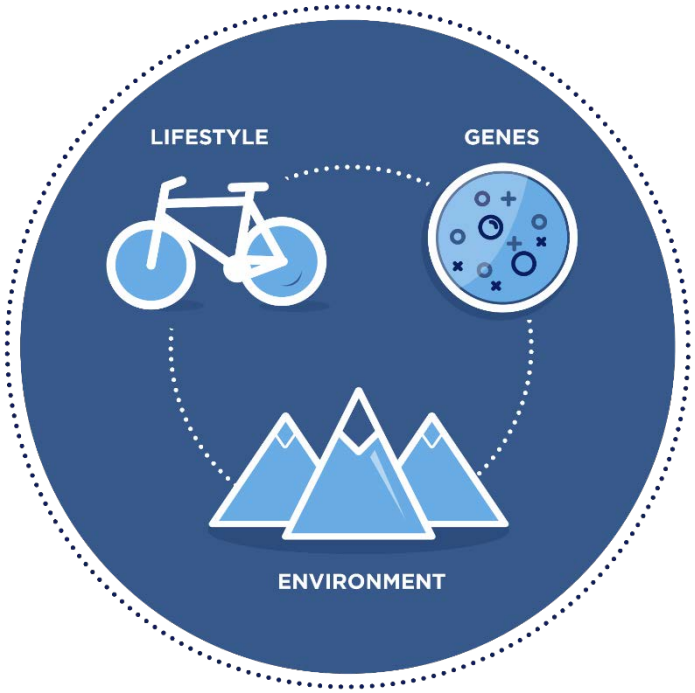
- Provide your name, phone number, and email address on the clipboard being circulated
- We will provide a web address and verification code. Please **agree to** the Informed and the Electronic Health Record consents, as well as, **complete** the health questionnaires
- We'll work with you to schedule your free in-person appointment located at the CTSC (Main hospital, Payson Tower, 2nd Floor)
- Provide physical measurements and specimens (blood, urine) at your appointment



- Receive a $25 American Express gift card when all enrollment steps are complete

The Value For Participants

- **$25** when all consents are agreed to and all steps in the process completed
- An **opportunity to learn** about your health indicators and receive access to your data
- An opportunity to **prevent disease** and improve the health of future generations
- The opportunity to **be part of a movement** to make our healthcare more precise, more personal, and more effective



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Any questions?