

9.5a From Clinical Genetics and Genomics to Precision Medicine

10x10 – Introduction to Biomedical Informatics & Artificial Intelligence
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From Clinical Genetics and Genomics to Precision Medicine

Genetic disorders

Genetic testing

Pharmacogenomics

Gene expression

Cancer genomics

Genomewide association studies

Polygenic risk scores

Biobanks

Consumer genomics

Precision Medicine

Genetic disorders

Involvement of one or more genes in human disease, simple or complex (Claussnitzer, 2020)

Many new technologies for determining genome (genotype), combined with growing amounts of clinical data (phenotype), provide opportunity to uncover genetic causes of disease (Collins, 2021)

Genetic risk factors have substantial impact on healthy life years (Jukarainen, 2022)

Growing advances and challenges for use in healthcare (Goranitis, 2025)

Catalog of human genetic disorders – [On-line Mendelian Inheritance in Man \(OMIM\)](#)

- Originally textbook, then part of NCBI system, now standalone Web site
- Over 28,000 entries from over 17,000 gene loci

[MedlinePlus Genetics](#) from NLM has consumer orientation

Monogenic disorders

Classic textbook genetics

If the DNA that codes for a protein contains an error, or mutation, it might result in an altered structure and, as a result, altered function, e.g.,

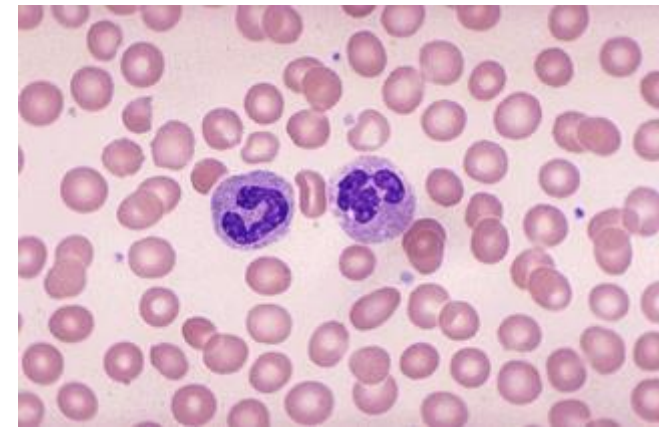
- Normal vs. sickle cell hemoglobin
- Huntington's Chorea (Huntington's Disease)

Sickle cell anemia

Homozygotes (Hgb SS) have “sickling” of blood cells causes painful crises

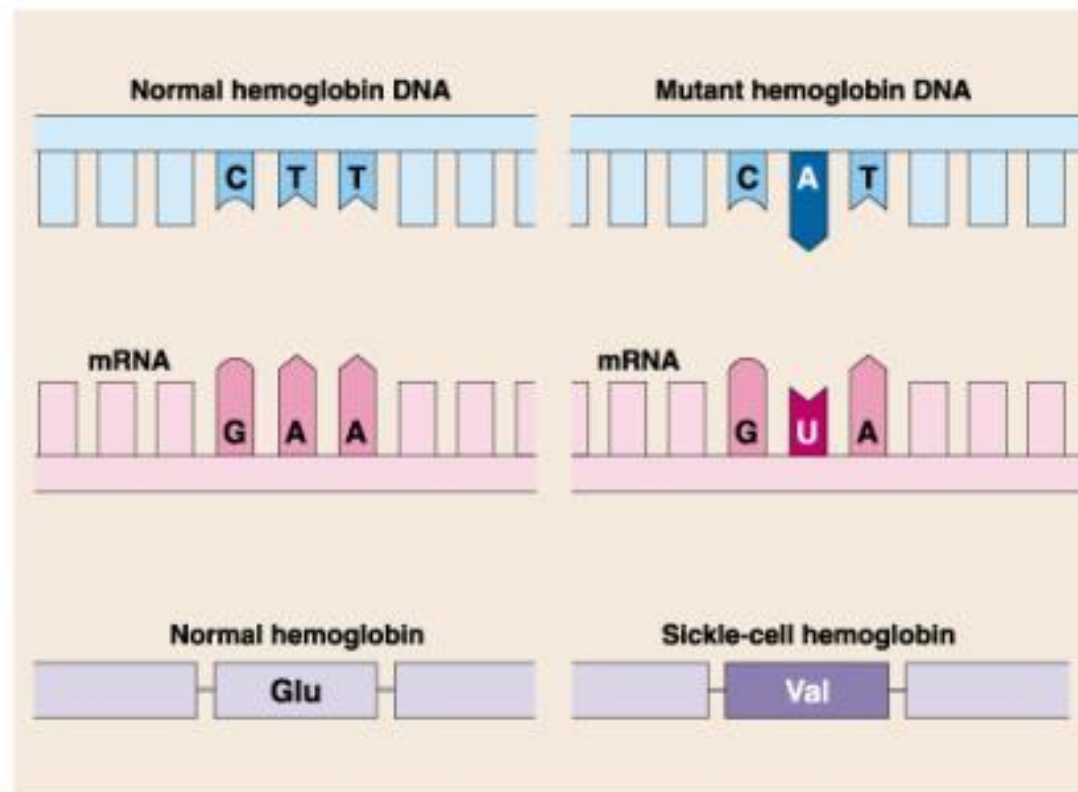


Heterozygotes (Hgb AS) have normal blood cells and increased resistance to malaria, which is one reason why gene persists in population



Normal vs. sickle cell hemoglobin

Substitution of one amino acid (valine for glutamic acid) in the 6th (of 146) position of gene for hemoglobin (WGBH, 2001)



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Huntington's Chorea

Progressive neurological disorder characterized by facial and/or extremity twitching as well as behavioral disorders

- Onset usually after age 35 (i.e., after reproductive years)

Cause of disease is an abnormal protein (huntingtin) that accumulates in brain

- Autosomal dominant gene with incomplete penetrance

Risk of disease (penetrance) associated with number of repeats in gene for huntingtin protein on chromosome 4

- <10-15 repeats is "normal"
- >35 leads to symptoms of disease likely to present
- Risk of early symptoms increases substantially when >38

Can be detected by test, but ethical dilemmas over if and when to have test

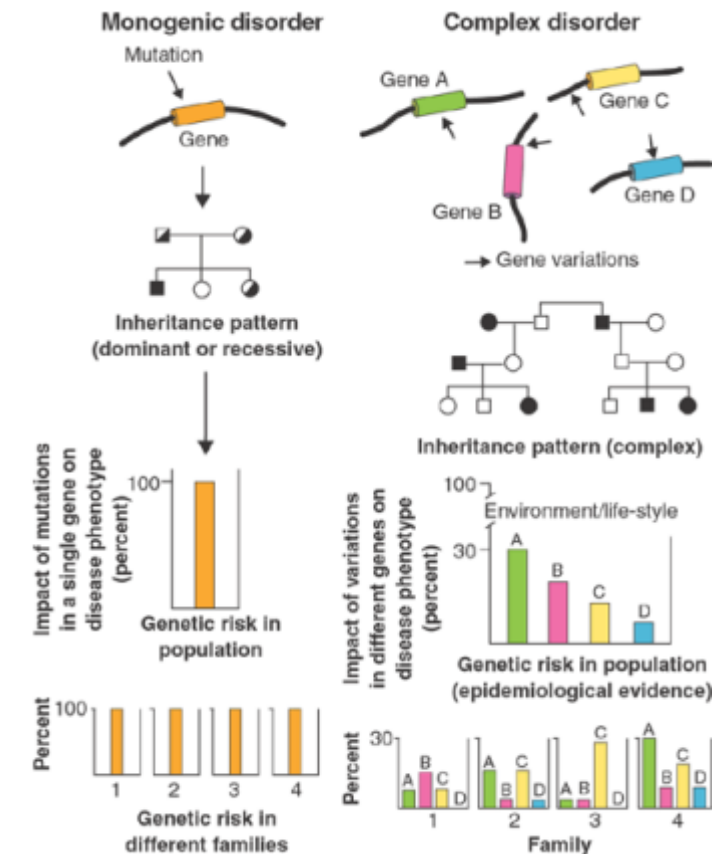
Complex genetic (polygenic) disorders

In many disorders there is trait heterogeneity, i.e., >1 gene causes disorder

In other disorders there is pleiotropy, i.e., 1 gene may cause >1 disease

In both single- and multi-gene disorders, they may be locus heterogeneity, i.e., variable expression within the trait

There may also be epistasis, which is the interaction between the genes at two or more loci, such that the phenotype differs from what would be expected if the loci were expressed independently



(Peltonen, 2001)

Examples of complex genetic disorders

BRCA1/BRCA2

- Increased risk in multiple types of cancer but related to family history (Nelson, 2019)

Color blindness

- Recall that Y chromosome determines sex
 - Females are XX and males are XY
- Most genes related to color vision reside on X chromosome
 - There are many genes, which influence vision of one or more colors
- Males are more likely to have color blindness (7% of men in US) because they only have one X chromosome

Genetic testing

Overview (Bourn, 2022)

Clinical best practices

- Preparing clinicians to “practice” genomic medicine (Crellin, 2019)
- Incidental findings should only be reported if “actionable” (Lee, 2025)
- [ACMG actionable list](#)

Actionable findings not uncommon

- eMERGE – ~3% (eMERGE Consortium, 2020)
- Iceland – ~4% (Jensson, 2023)
- Newborns – ~10% (Green, 2023)

Need policy for

- Return results to research participants – GA4GH (Lewis, 2021), AllOfUs (Venner, 2022)
- Handling variants of uncertain clinical significance (Burke, 2022)
- Increasing diversity in genetic studies (Fautumo, 2022)

Pharmacogenomics

Study of the genetic basis for variation in drug response

Genes influence

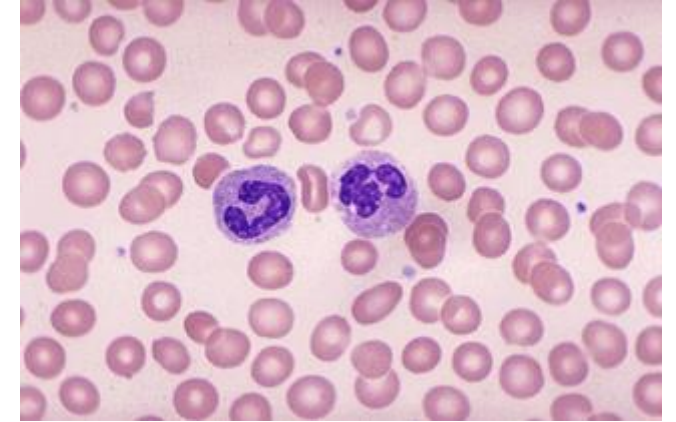
- Drug concentrations – how rapidly they are metabolized
- Drug target – how individuals respond

Genetic variation plays a significant role in variable response to drug therapy (Whirl-Carrillo, 2012)

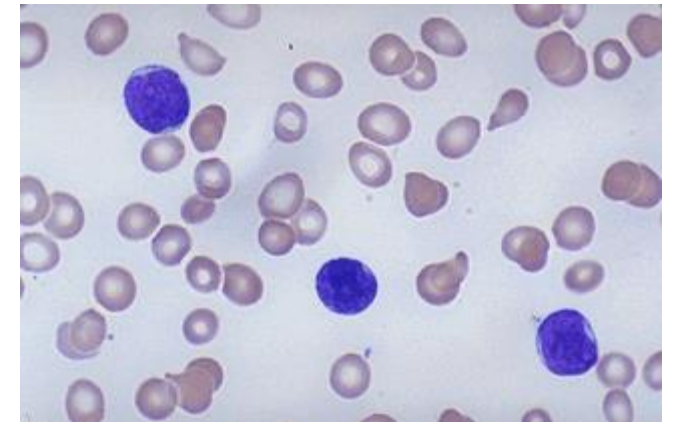
- Every clinician knows that patients respond differently to medications, sometimes along ethnic lines, which implies genetic relationship

6-mercaptopurine for childhood leukemia (Altman, 2002)

Normal – red blood cells and white blood cells



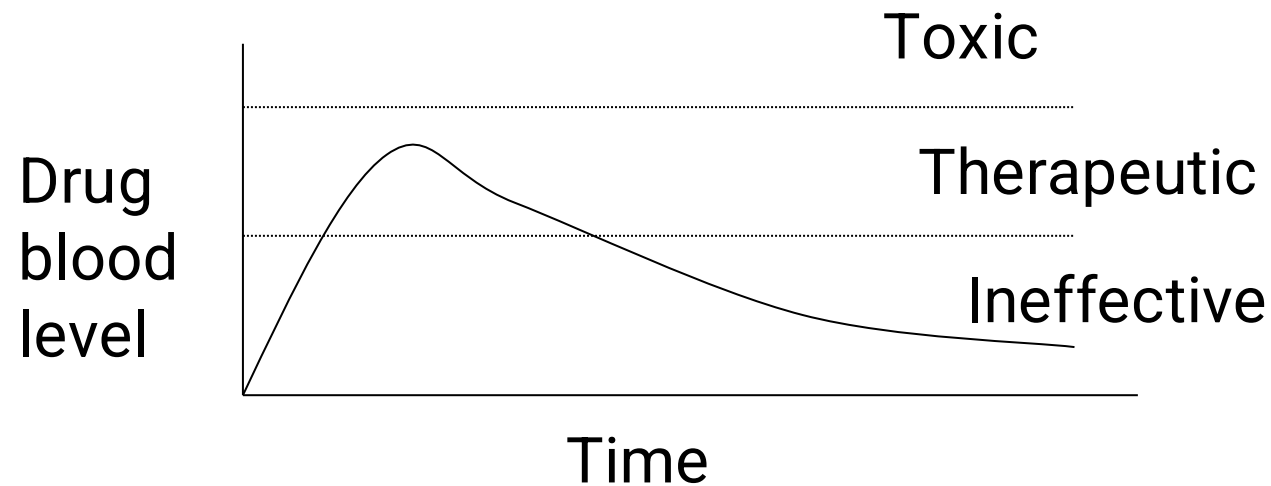
Leukemia – proliferation of abnormal white blood cells



Treatment of childhood leukemia is very effective

Chemotherapy agent 6-mercaptopurine has high cure rate

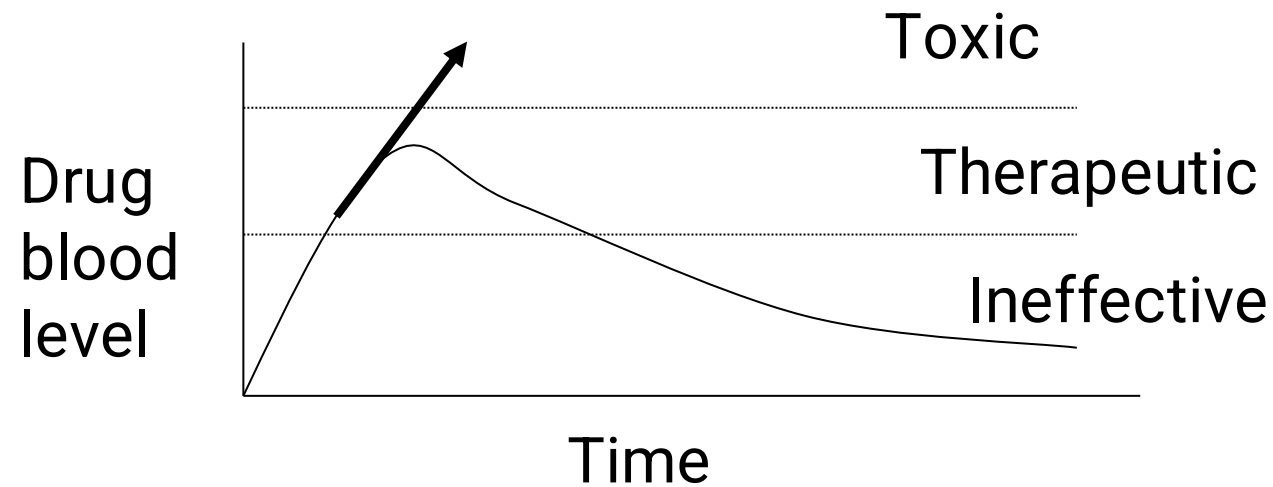
There is very narrow “therapeutic window” above which drug is toxic and below is ineffective



Except in a small number of children

In one out of 300 children, there is life-threatening bone marrow suppression

Drug metabolized by thiopurine methyltransferase (TPMT)



And is avoidable

Can test for defective TPMT gene before treatment

Those with defective gene can have dosage altered accordingly

A “prototype” case for pharmacogenomics, the study of variation in response to drugs due to genetic factors

Targeted therapy in chronic myeloid leukemia (CML)

In CML, chromosomes 9 and 22 break and fuse to form “Philadelphia chromosome”

Brings together two genes to form novel protein, BCR-ABL, which signals cells to proliferate

Blocked by imatinib mesylate (Gleevec), a prototype of “molecular-targeted” therapy (Druker, 2008)

- Highly focused drug has low toxicity

Additional agents added to progress (Foà, 2025)

Some drugs have selective response based on genetics

Gefitinib (Burotto, 2015)

- Found in clinical trials to only benefit 10% of patients with lung cancer, especially those from east Asia
- Patients who respond have mutant form of enzyme EGFR, associated with repeats of gene

Trastuzumab (Herceptin; Grassadonia, 2015)

- Women who overexpress HER-2 gene in breast cancer respond well to Herceptin, which blocks HER-2 protein that promotes cell proliferation

ALK inhibitors (Pacheco, 2018; Solomon, 2024)

- Patients with stage IV anaplastic lymphoma kinase gene rearrangement positive (ALK-positive) non-small cell lung cancer have longer survival

RNA-silencing (Zhnag, 2021)

- Patisiran for hereditary transthyretin amyloidosis (Adams, 2018)
- Givosiran for acute hepatic porphyrias (Balwani, 2020)



Application of pharmacogenomics

Many resources available

- ClinPGx – formerly PharmGKB (Klein, 2025)
- [FDA Table of Pharmacogenetic Associations](#)

Checklist for consideration of pharmacogenomics test (Beitelshees, 2011)

- Is there relationship between test results and response to drug therapy?
- Have initial results been validated?
- What is frequency of genomic variation in patient population?
- Is there clear course of action based on test result?
- What are benefits and harms to patient of modifying drug therapy?

Growing opportunities for use of AI in drug design (Heifetz, 2022; Swanson, 2024)

RCT in Europe of 12-gene pharmacogenetic panel significantly reduced incidence of clinically relevant adverse drug reactions (Sven, 2023)

Broad genomic profiling used only half of time when indicated (Wang, 2025)