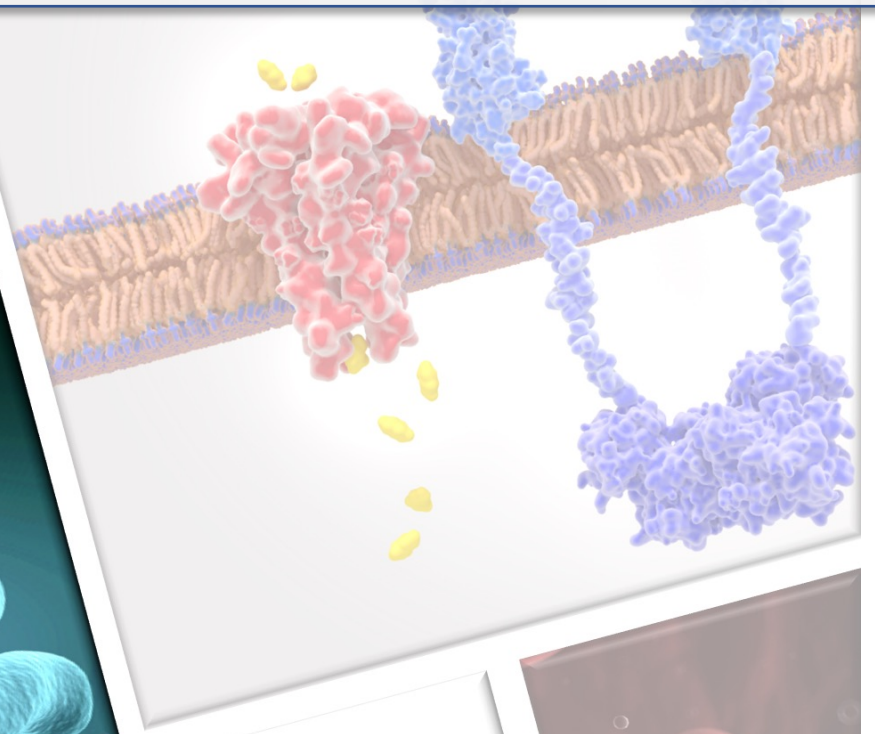
Imperial College London

Complex disease and Pharmacogenetics



Dr Chris John

Session Plan

Part 1

Complex genetic disease

Part 2

Pharmacogenetics/pharmacogenomics

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Session Plan

Part 1

Complex genetic disease

- Heritability / concept
- Twin studies
- Mendelian vs. complex disease
- Genome-wide association studies

Part 2

Pharmacogenetics

- Definition
- Differences in drug response
- How genes impact drug response

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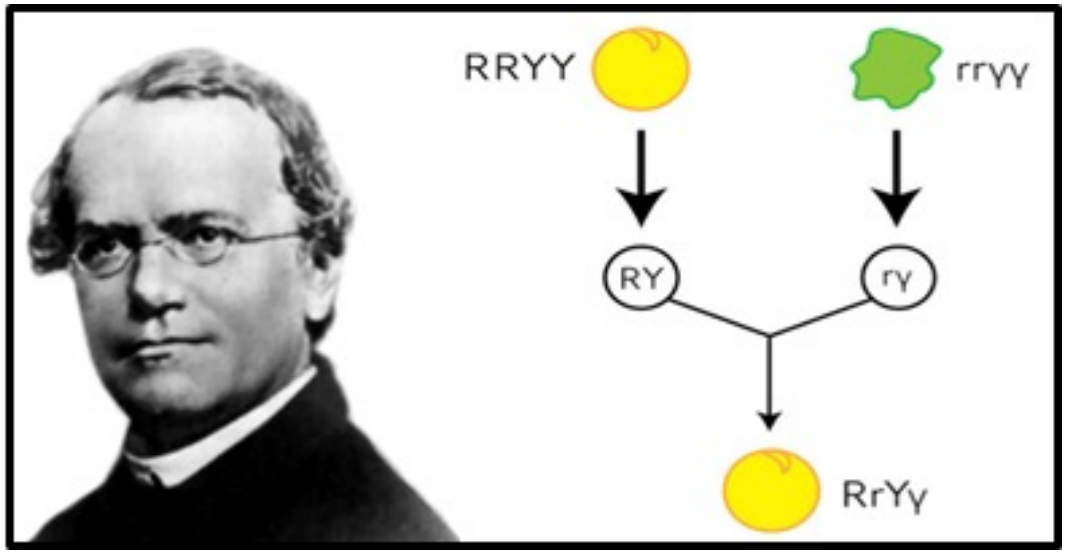
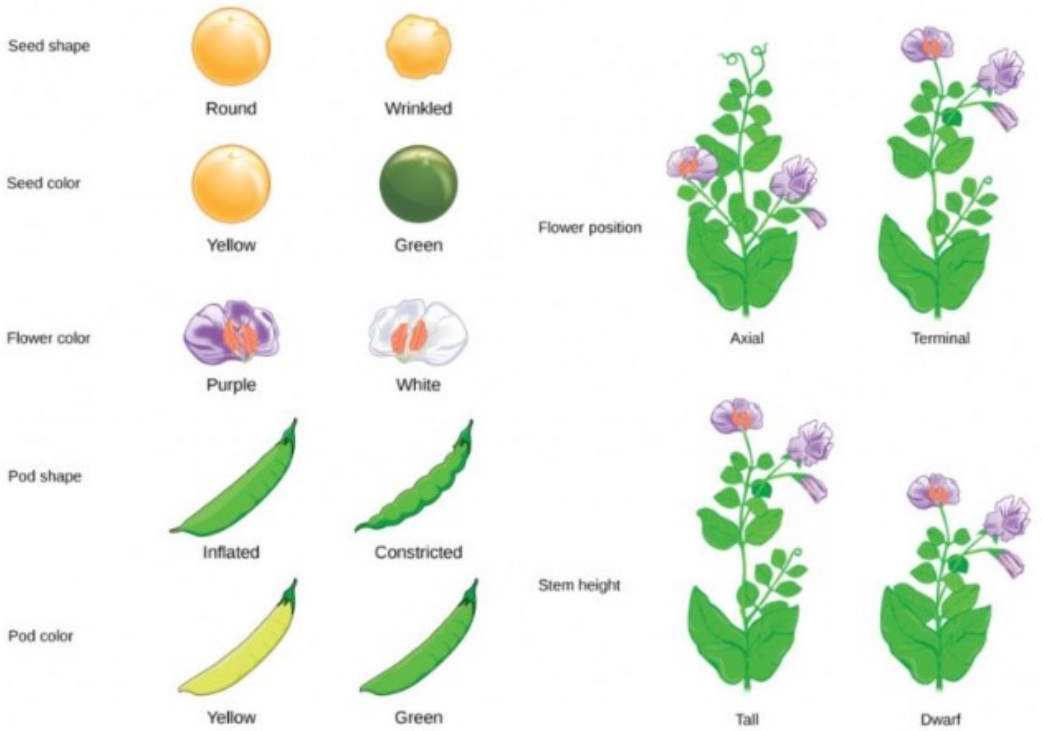
Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Mendelian Trait

- Classically - Controlled by **single gene**
- Inheritance follows Mendel's principles
  - This is simplified cf Phenotypic variability



https://opentextbc.ca/biology/chapter/8-1-mendels-experiments/



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Mendelian Trait

- Classically - Controlled by **single gene**
- Inheritance follows Mendel's principles
  - This is simplified cf Phenotypic variability

- Phenotypes easily identified in humans

Dominant?

Trait	Dominant Allele	Recessive Allele	Phenotypic Ratio in Offspring (F1 Generation)	Phenotypic Ratio in Offspring (F2 Generation)
Hair Color	Brown (B)	Blond (b)	All offspring have brown hair (Bb)	3:1 ratio of brown hair (BB or Bb) to blond hair (bb)
Tongue Rolling	Rolling (R)	Non-rolling (r)	All offspring can roll their tongue (Rr)	3:1 ratio of tongue rollers (RR or Rr) to non-rollers (rr)
Hitchhiker's Thumb	Hitchhiker's (H)	Straight (h)	All offspring have hitchhiker's thumb (Hh)	3:1 ratio of hitchhiker's thumb (HH or Hh) to straight thumb (hh)
Attached Earlobes	Attached (E)	Free (e)	All offspring have attached earlobes (Ee)	3:1 ratio of attached earlobes (EE or Ee) to free earlobes (ee)
Blood Type	Type A (IA)	Type O (i)	All offspring have blood type A (IAi)	3:1 ratio of blood type A or B (IAIA, IAi, IBi) to type O (ii)
Freckles	Freckled (F)	Non-freckled (f)	All offspring have freckles (Ff)	3:1 ratio of freckled (FF or Ff) to non-freckled (ff)
Bent Little Finger	Bent (B)	Straight (b)	All offspring have bent little finger (Bb)	3:1 ratio of bent little finger (BB or Bb) to straight (bb)
Eye Color	Brown (E)	Blue (e)	All offspring have brown eyes (Ee)	3:1 ratio of brown eyes (EE or Ee) to blue eyes (ee)
Dimples	Dimpled (D)	Non-dimpled (d)	All offspring have dimples (Dd)	3:1 ratio of dimpled (DD or Dd) to non-dimpled (dd)

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Mendelian Trait

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- Interlocking fingers- Controlled by **single gene?**
- **Left thumb on top dominant**

3:1

Left : Right

LL	LR
LR	RR

Parents	L offspring	R offspring	percent L
L x L	1252	880	59%
L x R	2309	2573	47%
R x R	1298	2815	32%

Complex Trait

- Most human traits are controlled by **two or more genes** and also influenced by environmental factors.
- **NOTE – don't follow predictable patterns of inheritance**

Quantitative traits

- Height (~12,000 genes/~ 80% genetic)
- Weight (~400 genes/~ 40-70% genetic)
- Intelligence (~10,000 genes/~ 30-70% genetic)
- Blood pressure (~1,000 genes/~ 30-60% genetic)

Complex disease

- Cardiovascular disease (e.g 'heart attack gene' – 50% ↑ risk)

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Mendelian Trait vs Complex Trait

- Separation artificial
- Really a continuum Mendelian trait– complex trait

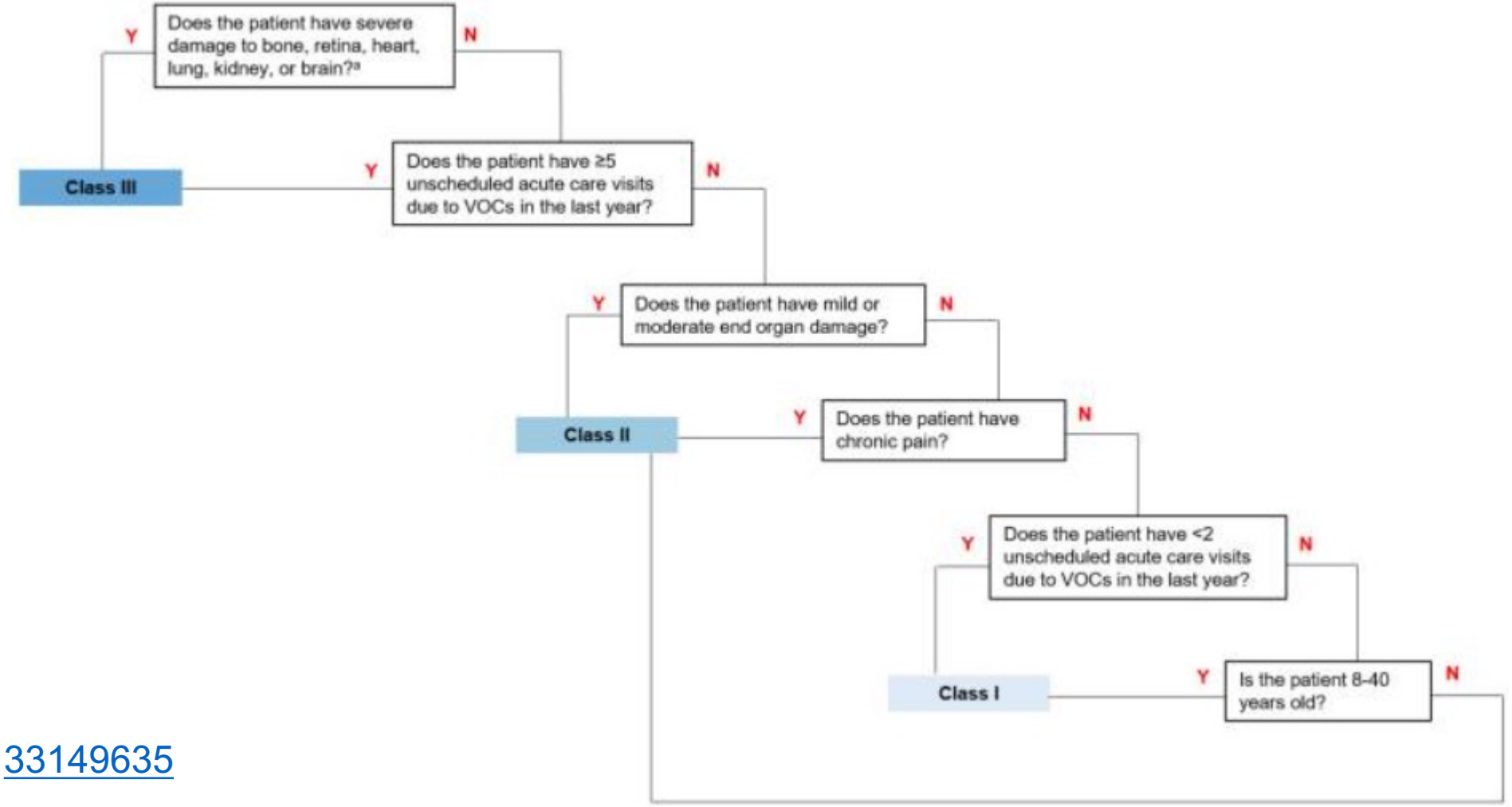
- Example – Sickle cell disease

- Point mutation in β-globin chain of the haemoglobin gene (Mendelian trait)
- Sickle Trait – mix of normal and sickle blood (codominant)
- Disease severity (i.e. phenotype) – mild to severe (other genetic loci)

- Epigenetics – Persistence of Foetal Haemoglobin (or POFH)
- Environment - temperature, altitude, air pollutants, diet, smoking

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Mendelian Trait vs Complex Trait



PMID: [33149635](https://pubmed.ncbi.nlm.nih.gov/33149635)

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Calculating Heritability

How much of our phenotypic differences are due to genetic differences? **(core objective of human genetics)**

NOTE: Nearly all traits are partially heritable

Causes of phenotypic differences

1. Genetic differences
2. Environmental differences

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Heritability: Phenotype vs Genotype - SNPs

- Single Nucleotide Polymorphisms: SNPs
- THEORY: Most common variation in human genome i.e. will account for the majority of polymorphism responsible for human disease

- 4-5 million per person
- Change in a single nucleotide in genetic sequence
- Can be in coding or non-coding region
- Even in non-coding region can have effect

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

Types of genetic association studies: 1 – Twin studies

How much of a trait is due to genetics vs. environment?

Why do some of my cupcakes taste more bitter than others?

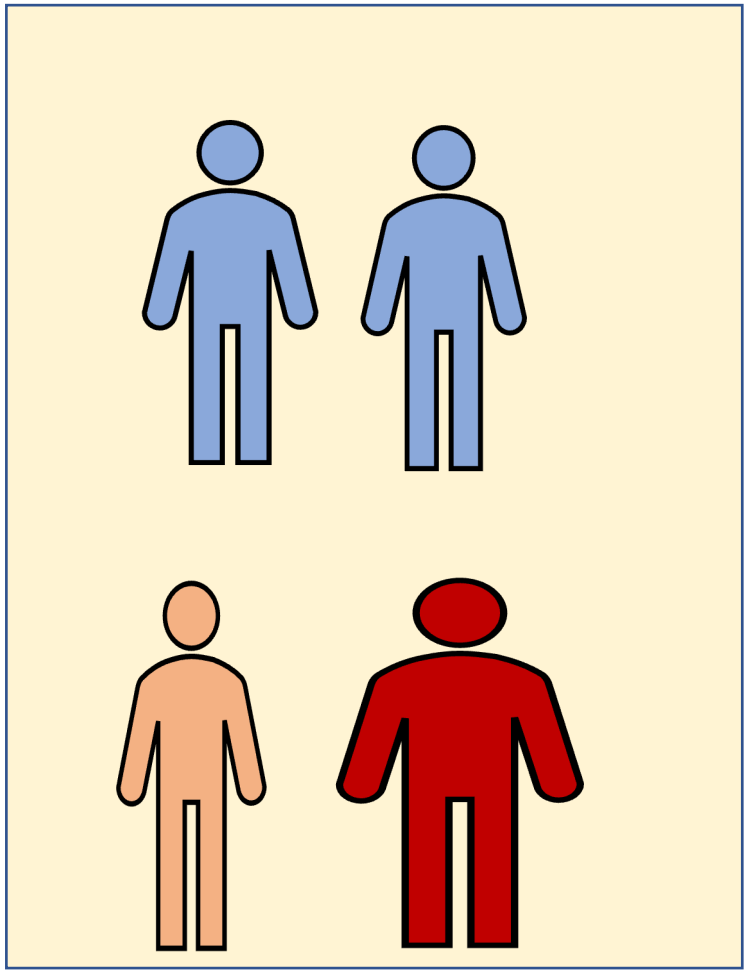
⅔ cup (83 g) flour
⅔ cup (133 g) white sugar
3 tbsp (20 g) cocoa powder
½ tsp baking soda
¼ tsp salt
½ cup (80 g) 50% dark chocolate
⅓ cup (72 g) vegetable oil
¼ cup (61 g) yoghurt
2 large eggs
1 tsp instant coffee powder
⅓ cup (78 g) hot water
2 tsp vanilla essence/extract

Types of genetic association studies: 1 – Twin studies

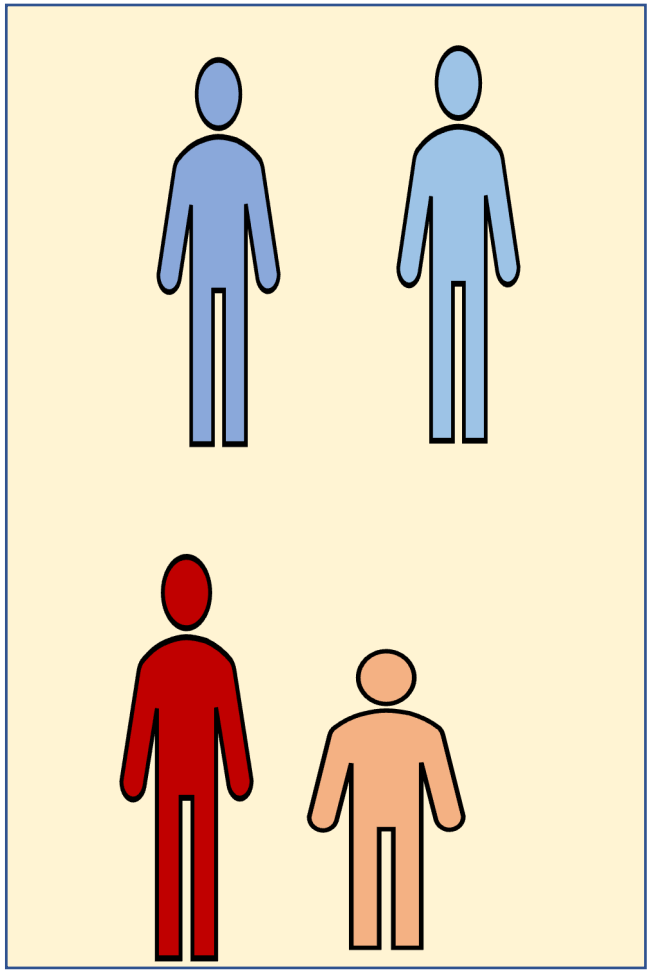
Monozygotic twins
100% shared genetic component

Dizygotic twins
50% shared genetic component

Weight



Height



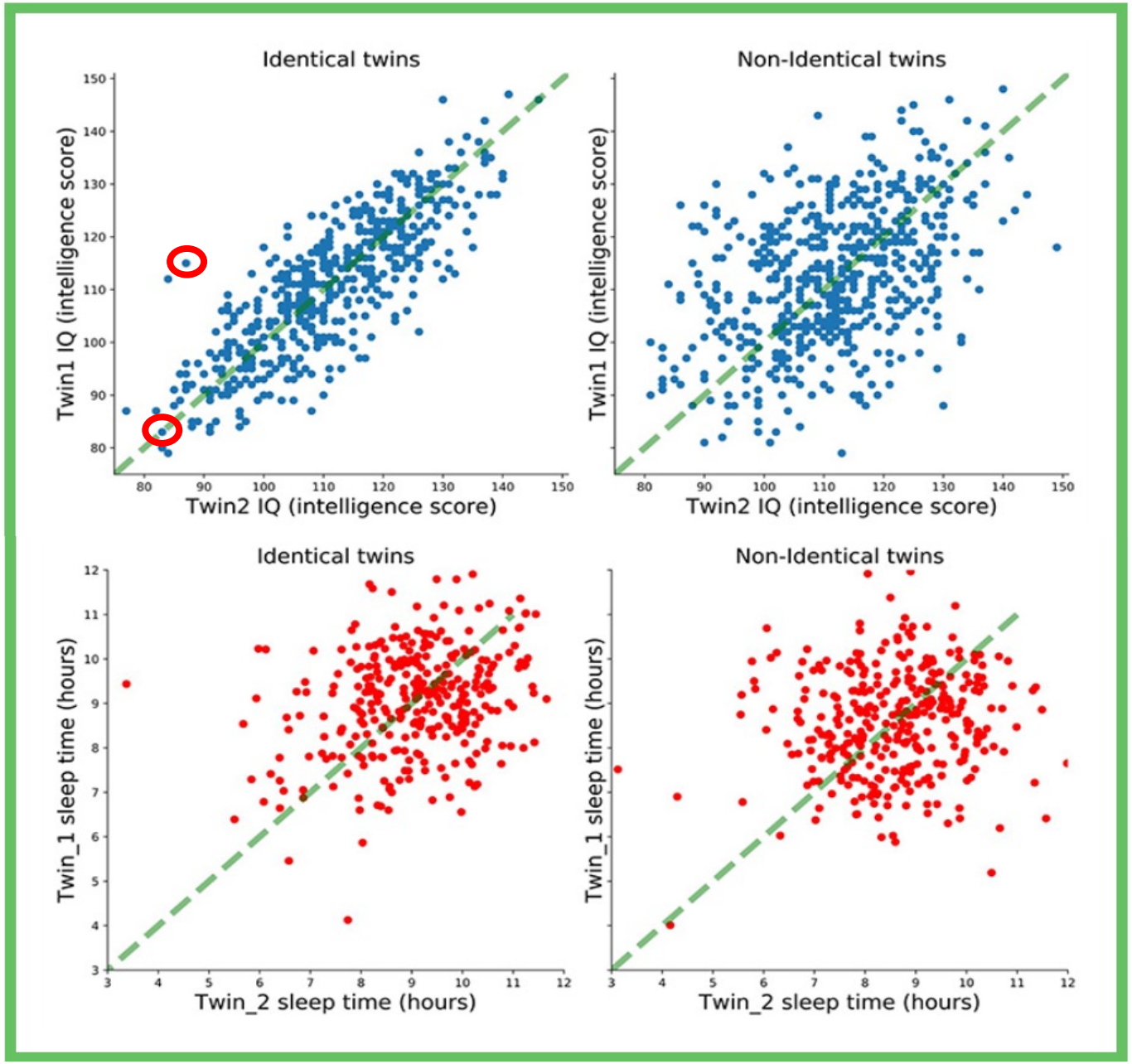
Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Twin Studies

Causes of phenotypic differences

1. Genetic differences
2. Environmental differences

THEORY:
MZ twins 100% genetically identical, so differences must be environmental

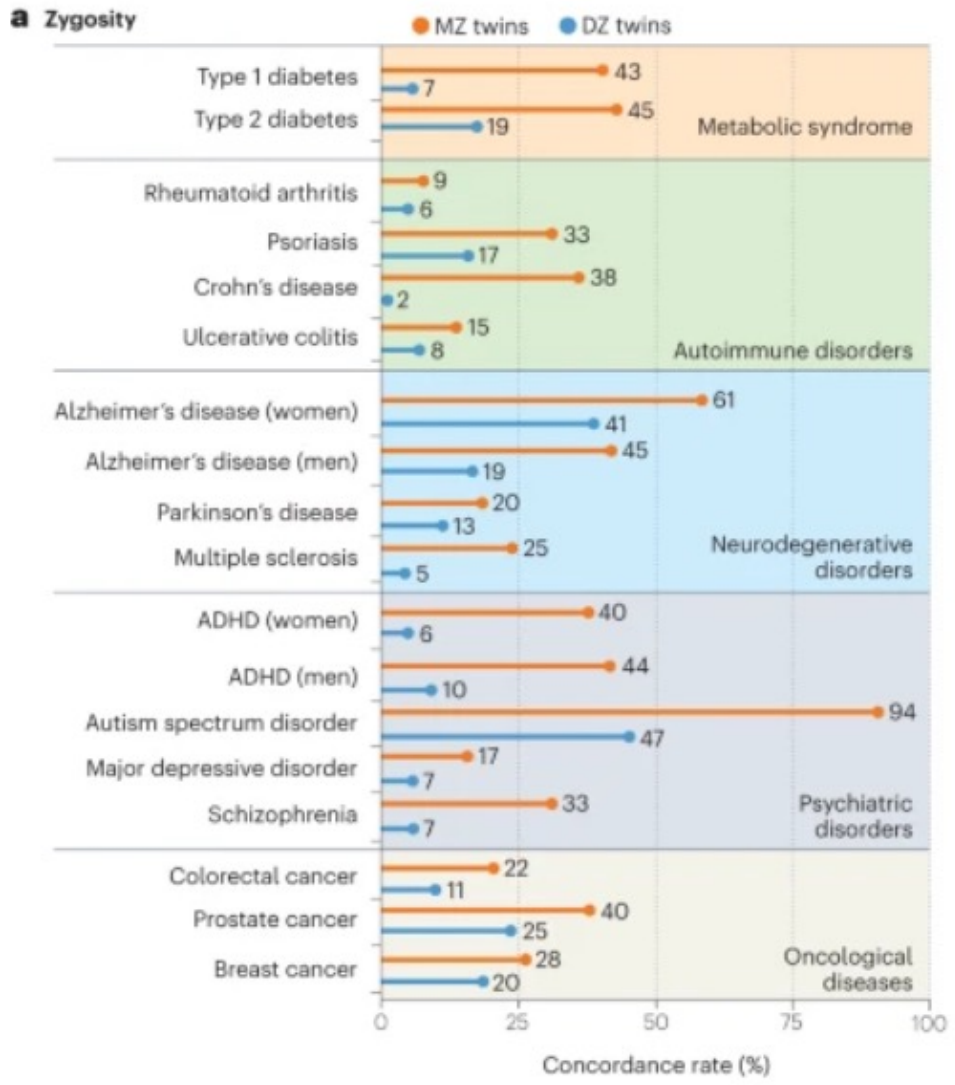


Moderate to high heritability

Low heritability

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Twin Studies



Heritability?

Concordance:
Both individuals in a pair have trait = concordant
One individual in pair has a trait and the other does not = discordant

e.g. if 99/100 MZ twins are concordant for eye colour, then eye colour would be almost entirely influenced by genetics

IMPT: Concordance is not absolute
e.g. could be due to shared or distinct environmental experiences

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

Twin Studies

PROBLEM:

Measure ‘Phenotype’.

Do not identify specific genetic variants that influence traits

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

Types of genetic association studies:
2 – Genetic association studies

Are specific genetic variants associated with a trait or disease

Why do some of my cupcakes taste more bitter than others?

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Types of genetic association studies:
2 – Genetic association studies
a) Candidate gene association studies

Are specific genetic variants associated with a trait or disease

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How to identify disease 'heritability?
2 - Genetic association studies

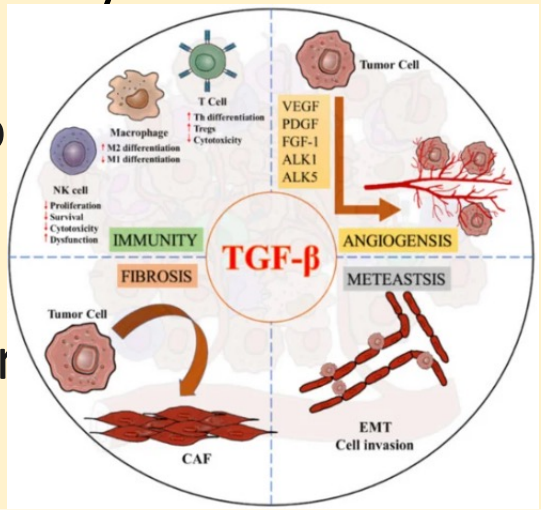
a) Candidate gene association studies (CGAS)

Analyse a few genes and variants based on knowledge that they have an important role in relevant normal physiology or disease pathophysiology (IMPT – Hypothesis driven)

EXAMPLE 1: Twin studies suggest several forms of cancer have high heritability

Normal physiology: TGF-β inhibits proliferation/promotes apoptosis (tumo
Cancer: Evidence that altered TGF-β signalling may affect cancer risk

CGAS: Studied association between SNPs for TGF-β gene and risk for cancer
association between *TGFB1* T29C SNP and breast cancer.



Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

How to identify disease 'heritability?
2. Genetic association studies

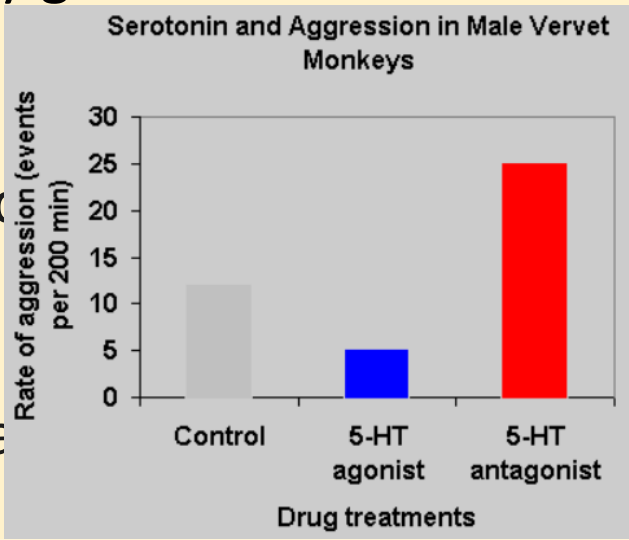
a) Candidate gene association studies (CGAS)

Analyse a few genes and variants based on knowledge that they have an important role in relevant normal physiology or disease pathophysiology (IMPT – Hypothesis driven)

EXAMPLE 2: Twin studies suggest 50% of aggression (trait) explained by genetics

Normal physiology: Dopamine/serotonin involved in impulse control
Increased aggression: Evidence that altered dopamine/serotonin breako
control and increases aggressive behaviours

CGAS: Studied association between SNPs for MAO gene and increased a
association between *MAOA rs6323*SNP and aggressive behaviour.



- Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

How to identify disease 'heritability?
2. Genetic association studies

a) Candidate gene association studies (CGAS)

Problems:
Limit the analysis to a relatively few number of pre-specified genes (large amount of genome ignored – believed to be ~ 15 million SNPs)

Biased towards genes and 'known' biological pathways (selection bias)

Alleles may differ between cases and controls but be unrelated to disease

Can't discover novel biology

- Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease

Types of genetic association studies:
2 – Genetic association studies
b) Genome Wide Association Studies (GWAS)

Are specific genetic variants associated with a trait or disease

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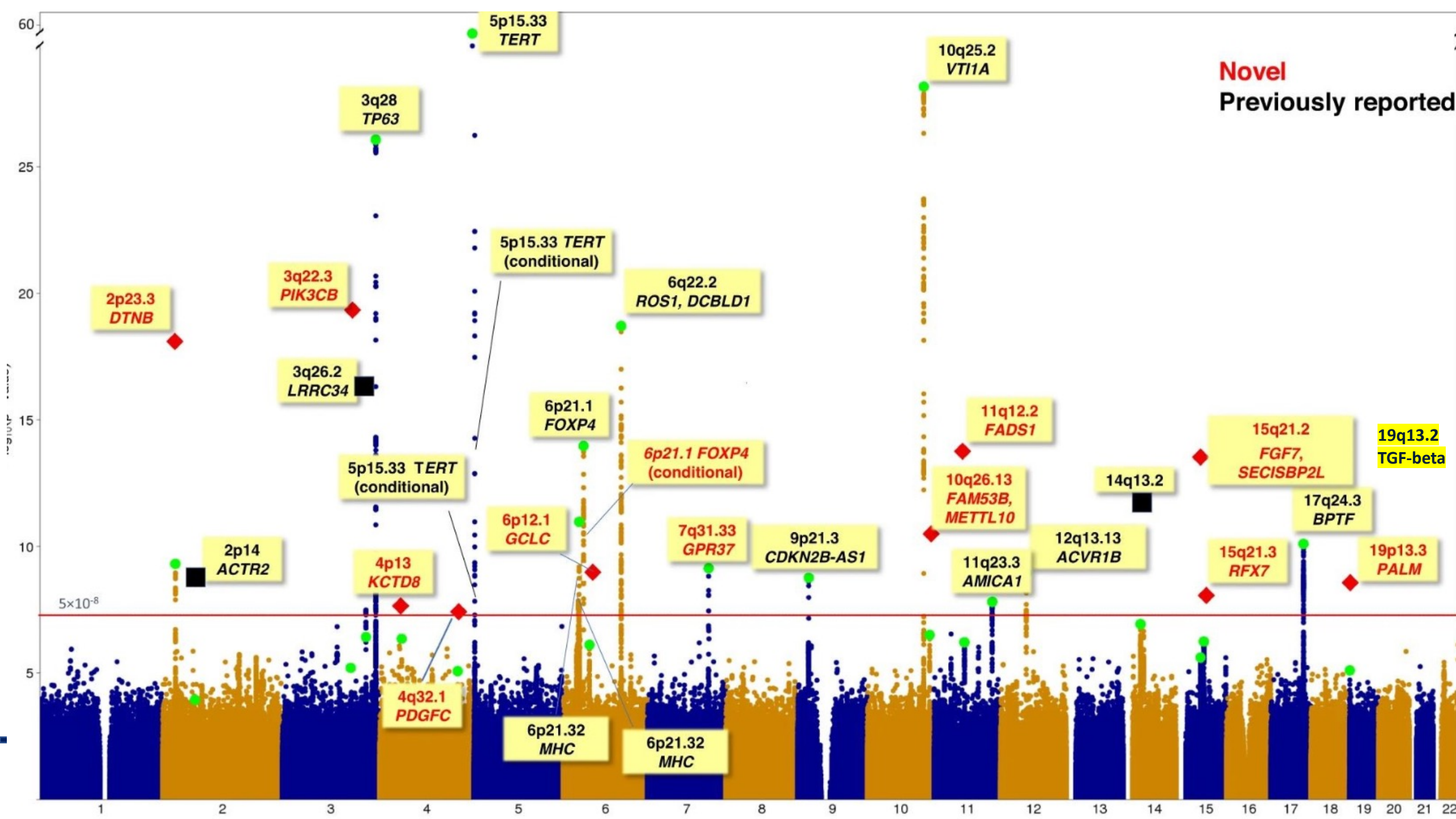
How to identify disease 'heritability?
2. Genetic association studies

b) Genome Wide Association Studies (GWAS)

Analyse 21,000 protein coding genes and ~ 1 million SNPs in human genome
(IMPT – Hypothesis free)


Novel
Previously reported
5p15.33 TERT
10q25.2 VTI1A
3q28 TP63
5p15.33 TERT (conditional)
3q22.3 PIK3CB
2p23.3 DTNB
6q22.2 ROS1, DCBLD1
3q26.2 LRRC34
6p21.1 FOXP4
11q12.2 FADS1
15q21.2 FGF7, SECISBP2L
19q13.2 TGF-beta
6p21.1 FOXP4 (conditional)
5p15.33 TERT (conditional)
10q26.13 FAM53B, METTL10
14q13.2
17q24.3 BPTF
6p12.1 GCLC
7q31.33 GPR37
9p21.3 CDKN2B-AS1
12q13.13 ACVR1B
2p14 ACTR2
4p13 KCTD8
11q23.3 AMICA1
15q21.3 RFX7
19p13.3 PALM
5×10-8
4q32.1 PDGFC
6p21.32 MHC
6p21.32 MHC
60
25
20
15
10
5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

How to identify disease ‘heritability?
2.

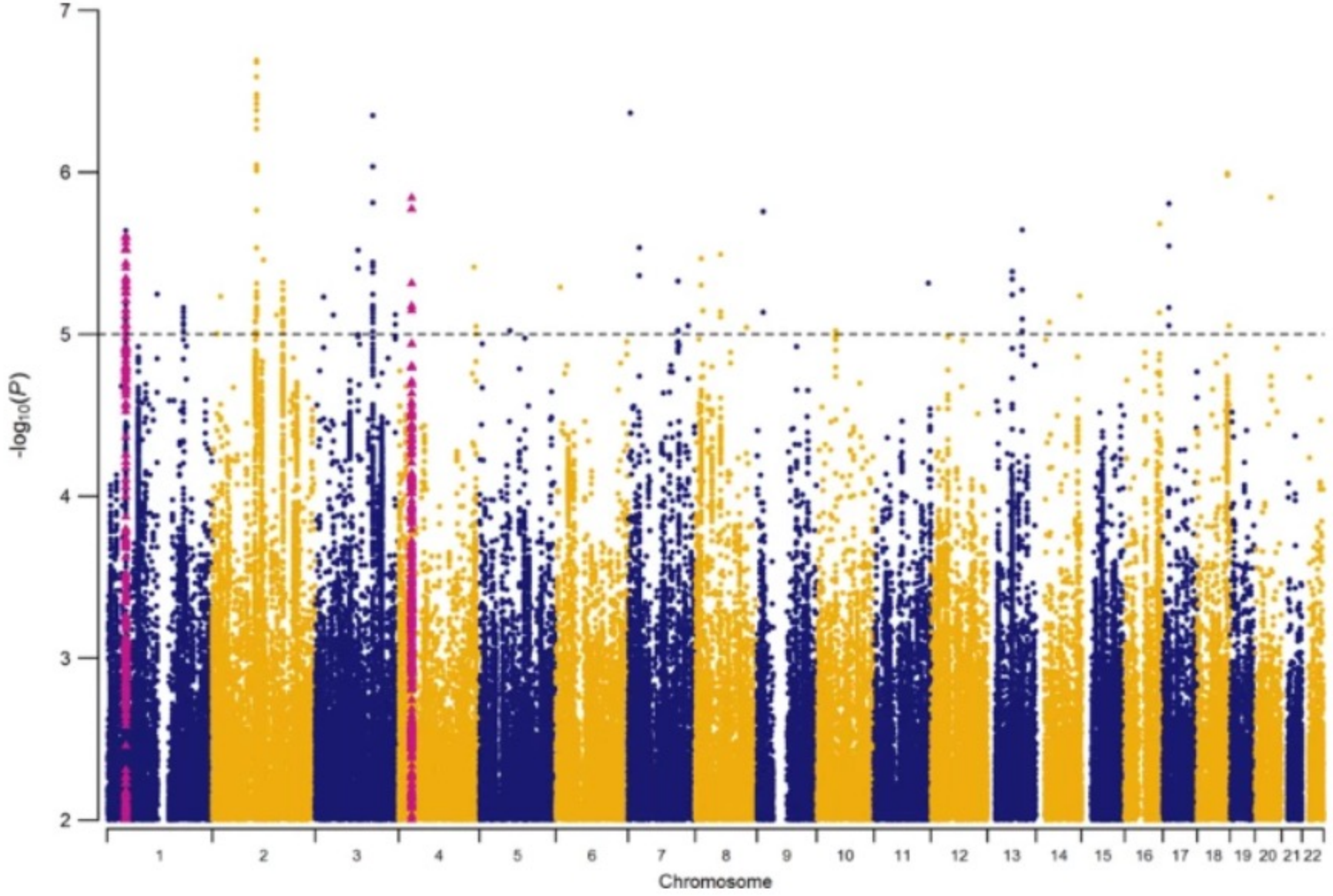
b) Genom

Analyse 21,0
(IMPT – Hyp

EXAMPLE 2:

CGAS: Studie
association b

GWAS: Ident
synaptic den



Significant

post-

How to identify disease 'heritability?
2. Genetic association studies

b) Genome Wide Association Studies (GWAS)

Benefits:
1. Can identify SNP-variant associations i.e. risk loci for complex disease
2. Identify at risk individuals
3. Discovery of novel biological mechanisms
4. Inform drug discovery or repurposing
5. Identify ethnic differences

Limitations:
1. Doesn't identify causal variants – further testing required
2. Can't identify all heritability ('missing heritability')
3. Thresholds – won't identify rare variants
4. Environmental influence - epigenetics

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Types of genetic association studies:
2 – Genetic association studies
c) Whole genome sequencing

Are specific genetic variants associated with a trait or disease

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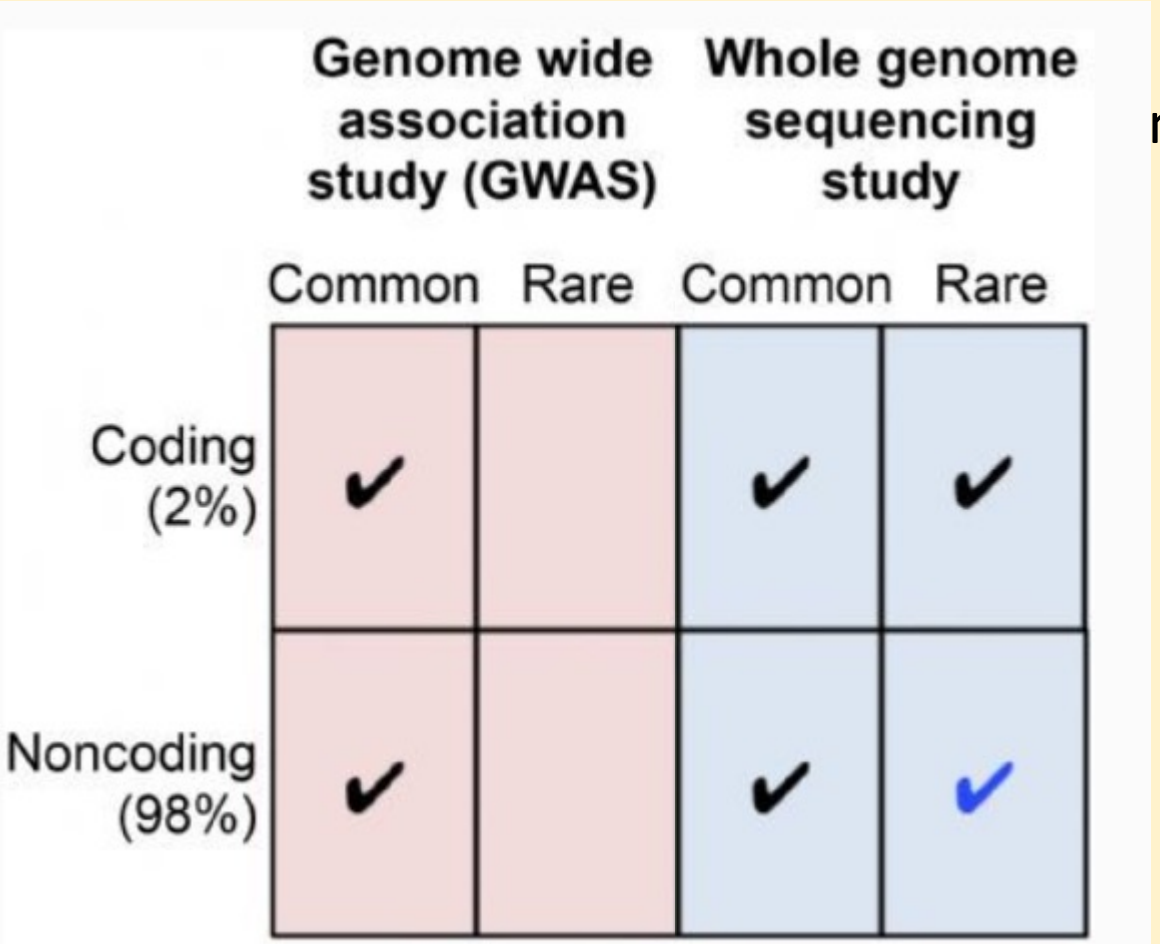
Molecular level

How to identify disease 'heritability?
2. Genetic association studies

c) Whole genome sequencing

- Provides informati me – 3000 times more data than GWAS
- Most GWAS use ar omit rare variants
- WGS: Entire geno including non coding regions
- Clear identificatior
- Roles of many gen



Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

How to identify disease 'heritability?
2. Genetic association studies

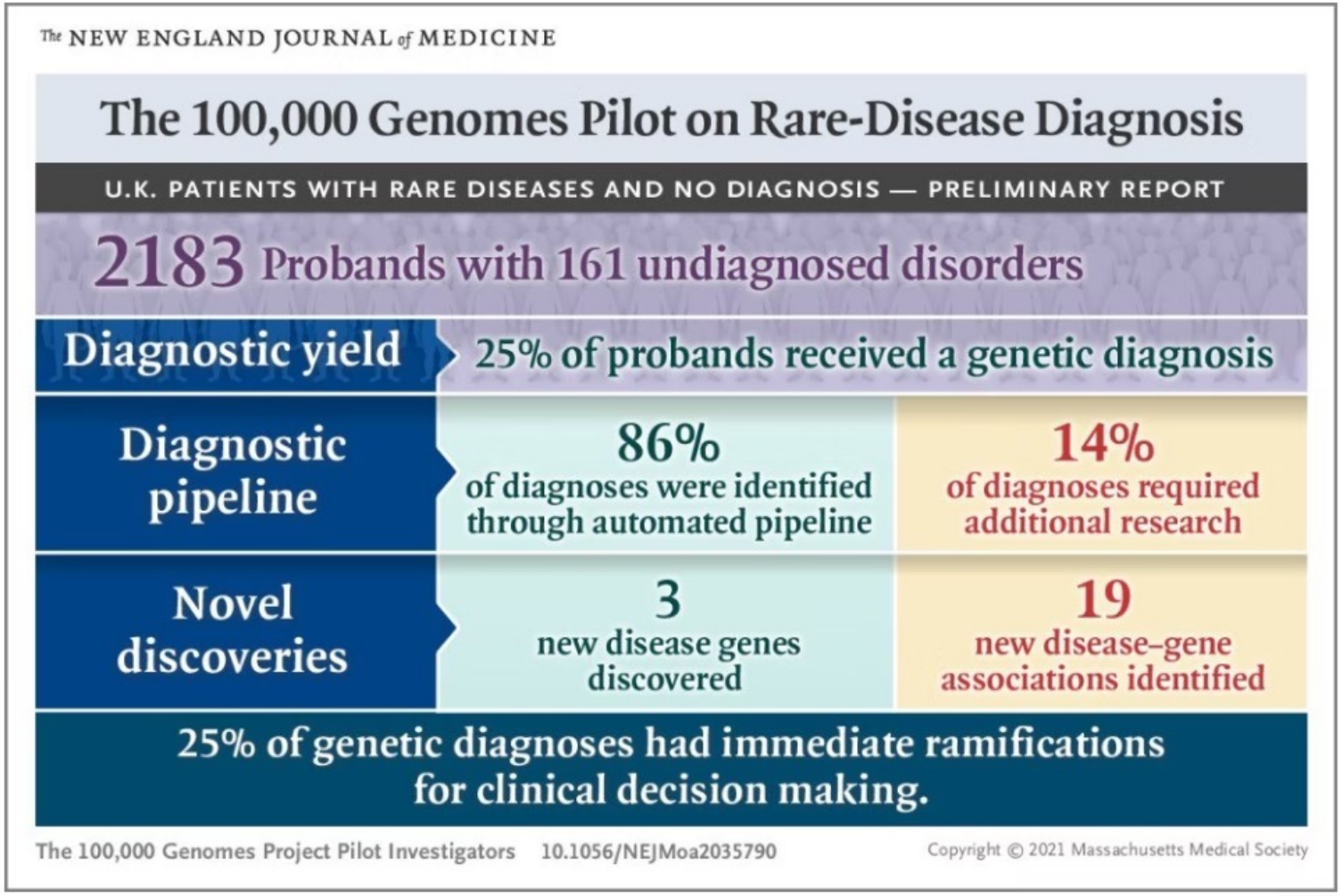
CGAS vs GWAS vs WGS

- Imagine a codon is a word in a book
- A sequence is a sentence
- A gene is a page from a book

- CGAS – will allow you to look at several pages of the book
- GWAS – will allow you to look at several chapters of the book
- WGS – will allow you to read the whole book

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

100,000 Genome Project



The NEW ENGLAND JOURNAL of MEDICINE

The 100,000 Genomes Pilot on Rare-Disease Diagnosis

U.K. PATIENTS WITH RARE DISEASES AND NO DIAGNOSIS — PRELIMINARY REPORT

2183 Probands with 161 undiagnosed disorders

Diagnostic yield	25% of probands received a genetic diagnosis	
Diagnostic pipeline	**86%** of diagnoses were identified through automated pipeline	**14%** of diagnoses required additional research
Novel discoveries	**3** new disease genes discovered	**19** new disease–gene associations identified

25% of genetic diagnoses had immediate ramifications for clinical decision making.

The 100,000 Genomes Project Pilot Investigators 10.1056/NEJMoa2035790

4660 participants

WGS led to a new diagnosis for 25% of the participants. Of these new diagnoses, 14% were found in regions of the genome that would be missed by other conventional methods, including other types of non-whole genomic tests.

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Progress Check

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Part 1

- Mendelian diseases are controlled by a single gene and complex diseases are controlled by multiple genes
- Genome-wide association studies analyze association between millions of SNPs throughout the genome with a complex disease
- Detect risk alleles or protection alleles
- Moving into era of whole genome sequencing

Part 2

- Different people respond differently to the effect of medications
- Genetic factors influence the way individuals respond to medication

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Session Plan

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Complex genetic disease

Part 2

Pharmacogenetics/pharmacogenomics

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- Differences in drug response
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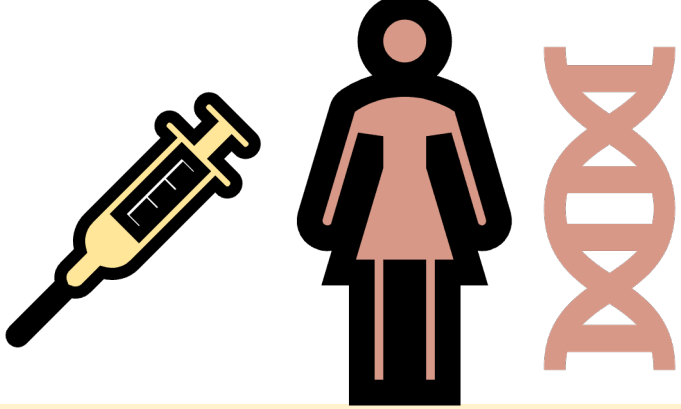
Pharmacogenomics

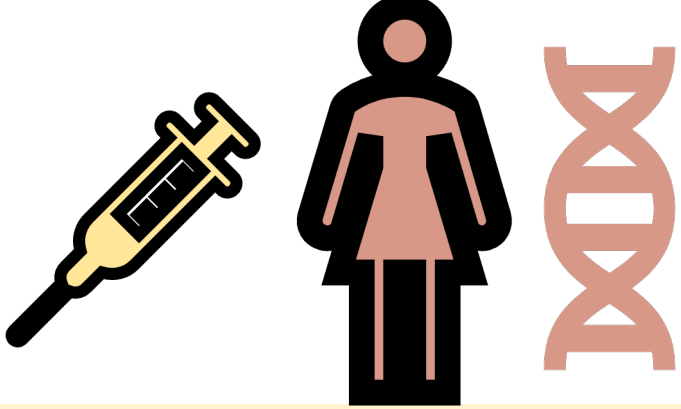


The study of variability in drug response due to genetic differences

This can be:
Pharmacodynamic – how a drug effects the body (efficacy)
Pharmacokinetic – how the body affects the drug (ADME)

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Pharmacogenomics



The study of variability in drug response due to genetic differences

THE PROBLEM: "One drug fits all"

Pharmacodynamic – how a drug effects the body (efficacy)

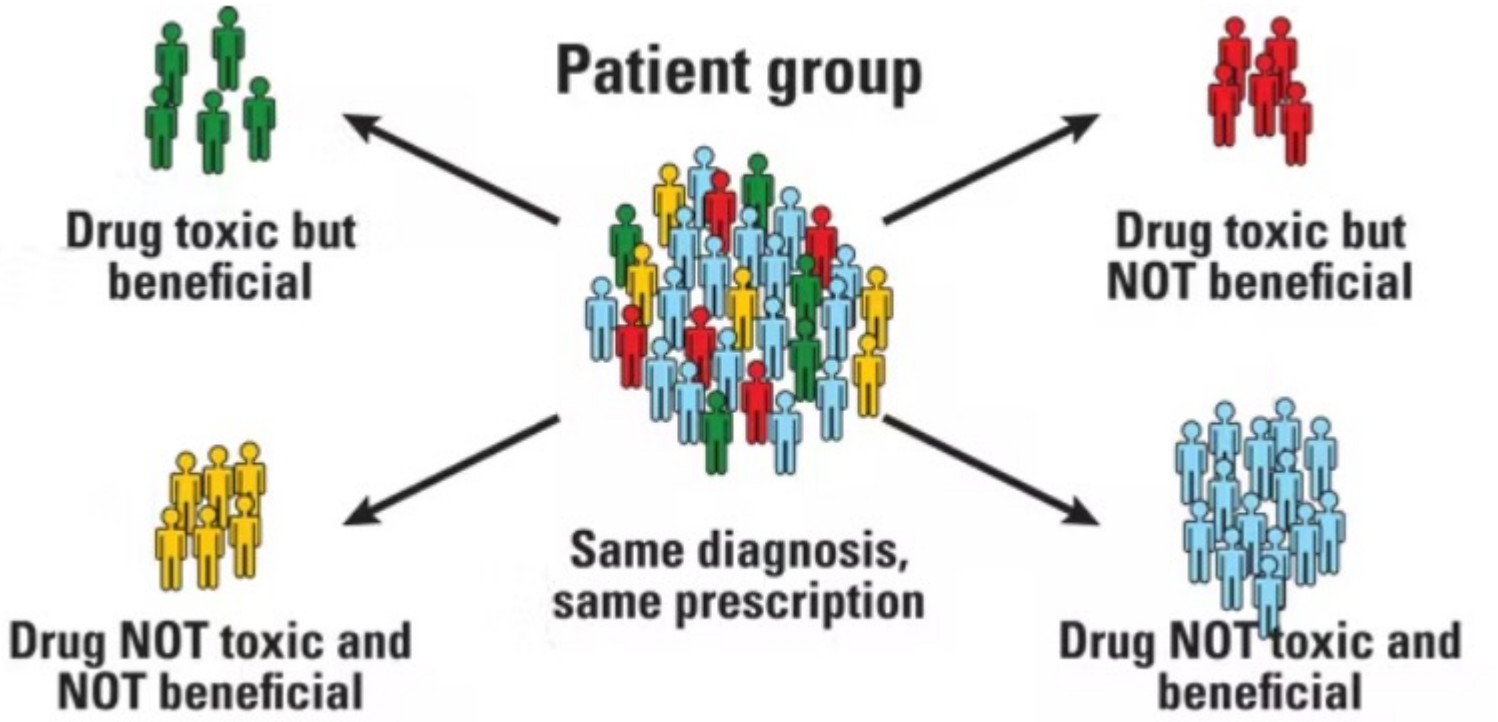
Estimate - ~90% of drugs only work in ~50% of people

Pharmacokinetic – how the body affects the drug (ADME)

Side effects (adverse drug reactions) – cause of ~7% of hospital admissions

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

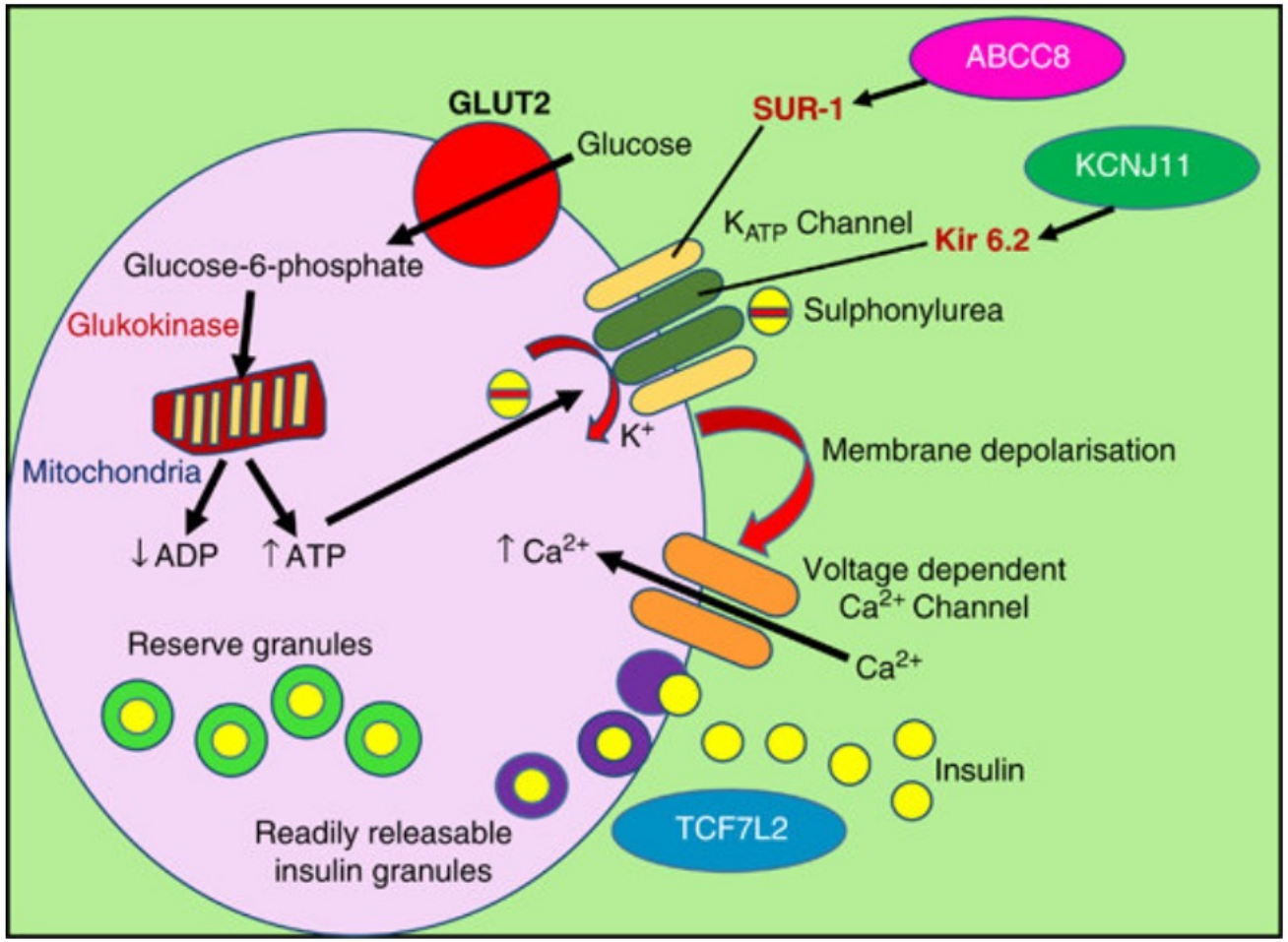
Influence of genes



Genetic variants in drug-related genes are very rare ($f < 0.1\%$) and thus will likely not be observed in clinical trials.

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Pharmacogenomics



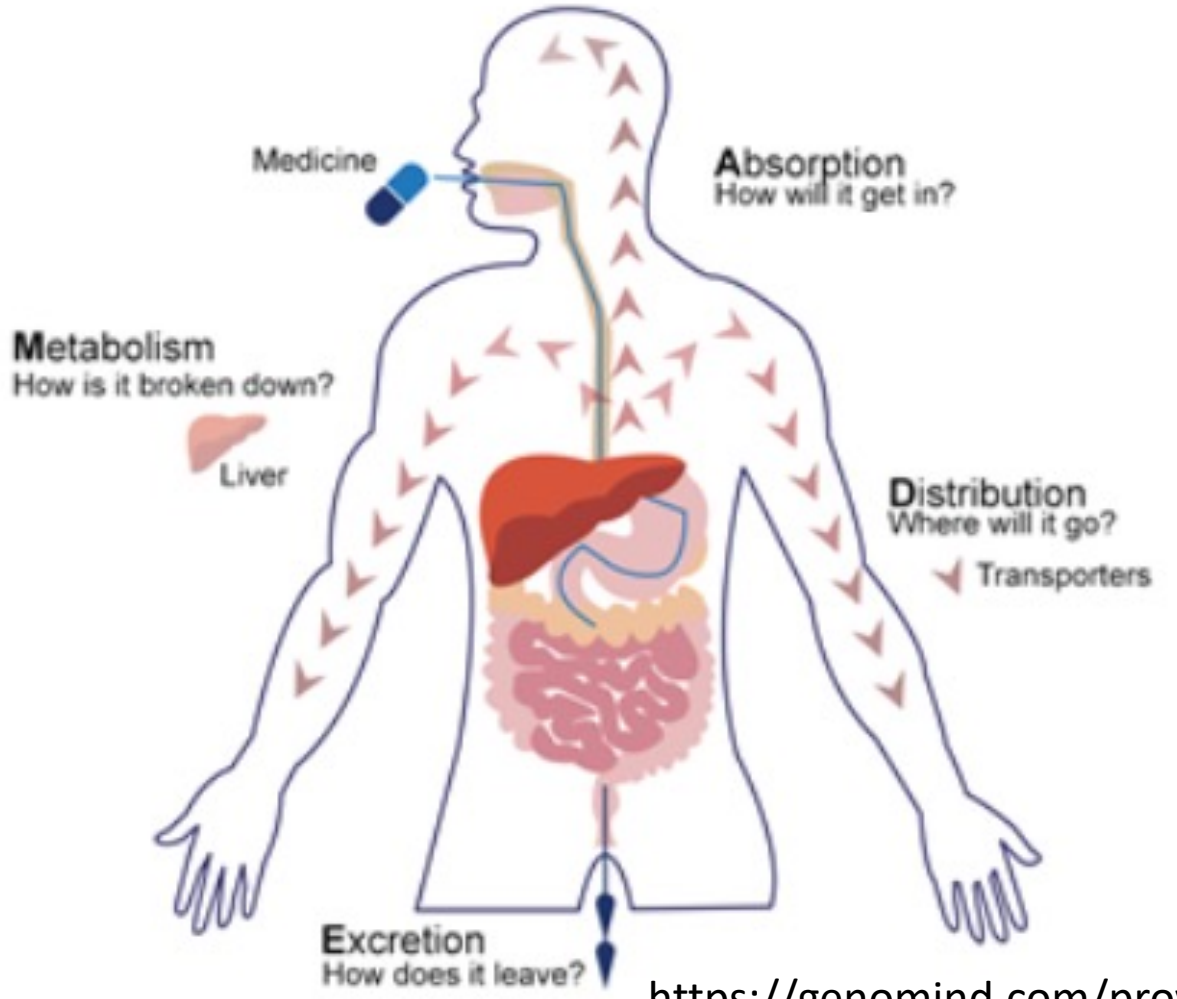
Pharmacodynamics – how a drug affects the body

DIFFICULT – need good understanding of drug action at the molecular level

Sulphonylurea induced hypoglycaemia in 1/3 of type 2 diabetes patients

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Pharmacogenomics



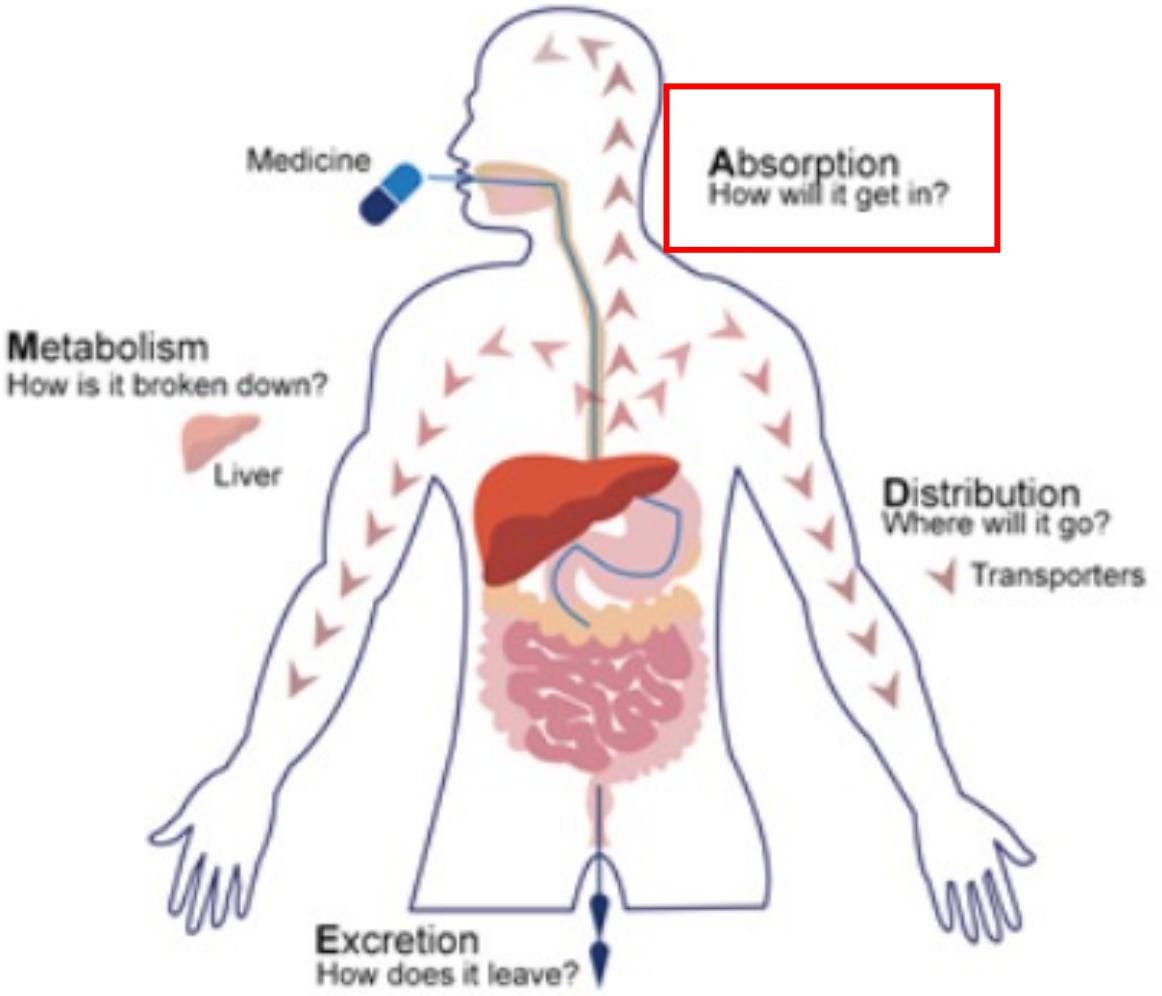
Pharmacokinetic – how the body affects the drug (ADME)

EASIER – monitor increase/decrease in blood/urine levels

https://genomind.com/providers/introduction-to-pharmacokinetics-four-steps-in-a-drugs-journey-through-the-body/

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

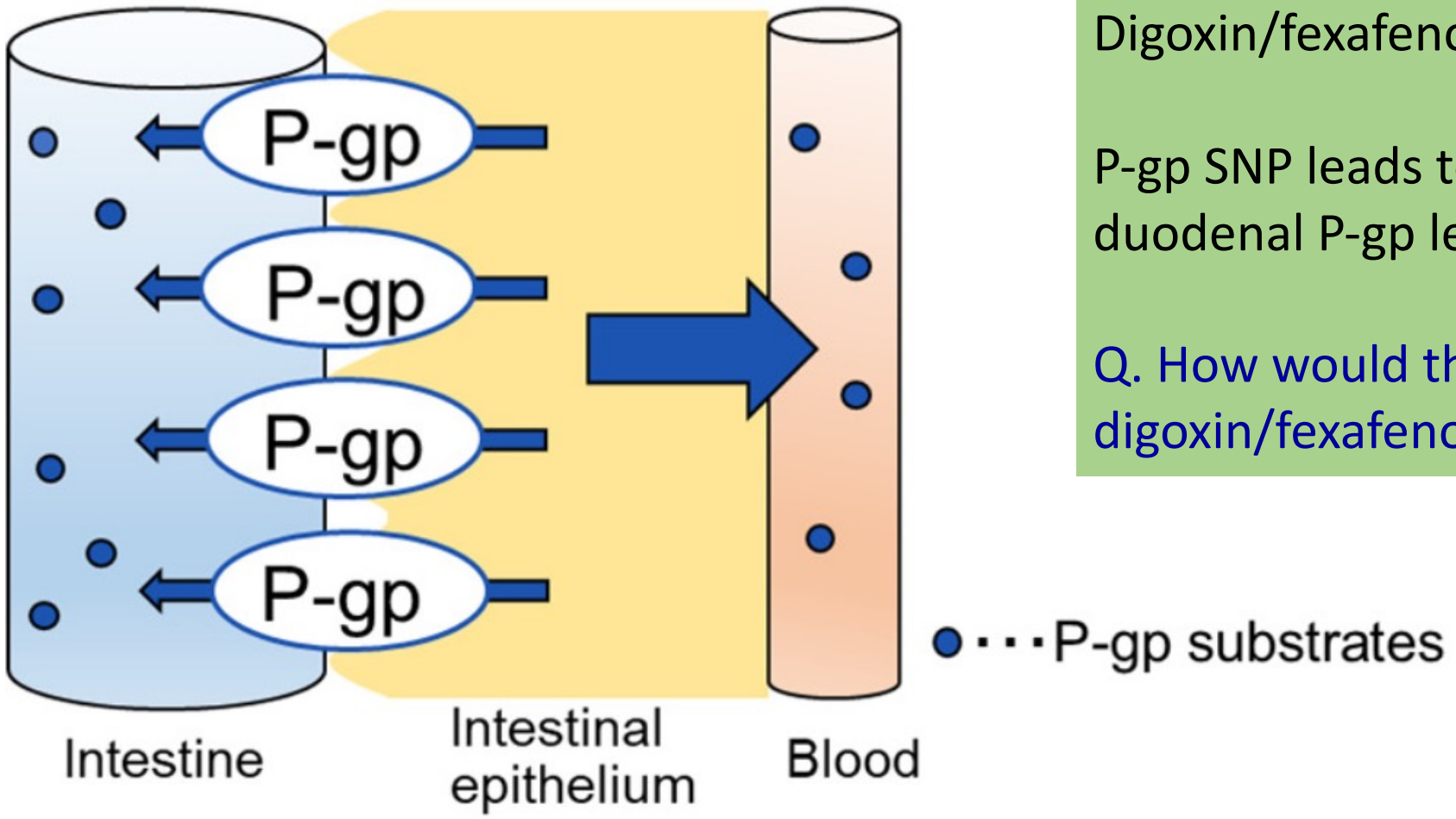
Absorption



- The majority of drugs are given orally
- Majority of drugs are absorbed in small intestine
- Use specific transporter proteins
- Wide variety of transporters used – although transporters can increase absorption or enhance removal

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Absorption



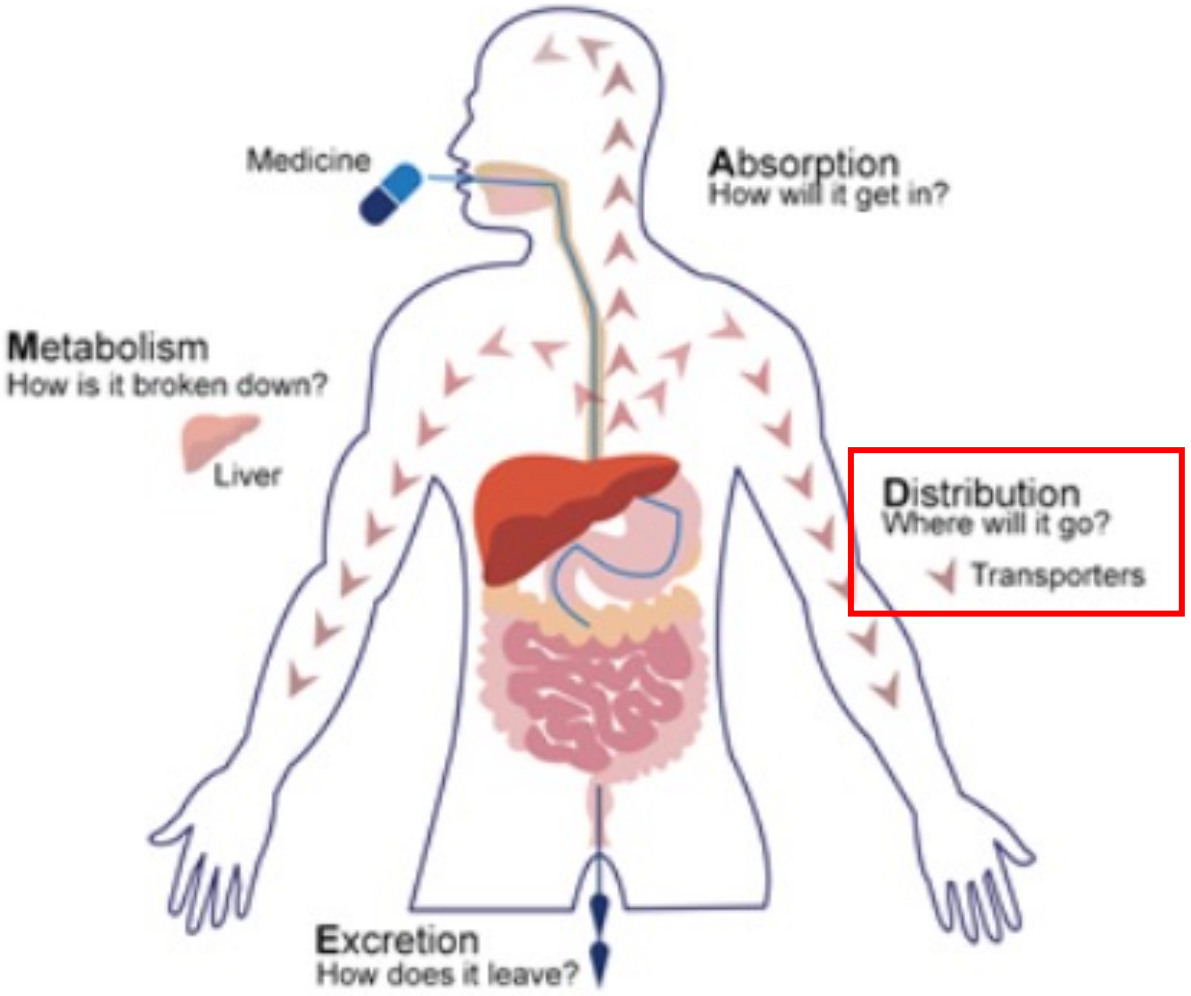
Digoxin/fexafenodine – substrates for P-gp

P-gp SNP leads to 2 fold decrease in duodenal P-gp levels

Q. How would this influence the effect of digoxin/fexafenodine in the body?

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Distribution

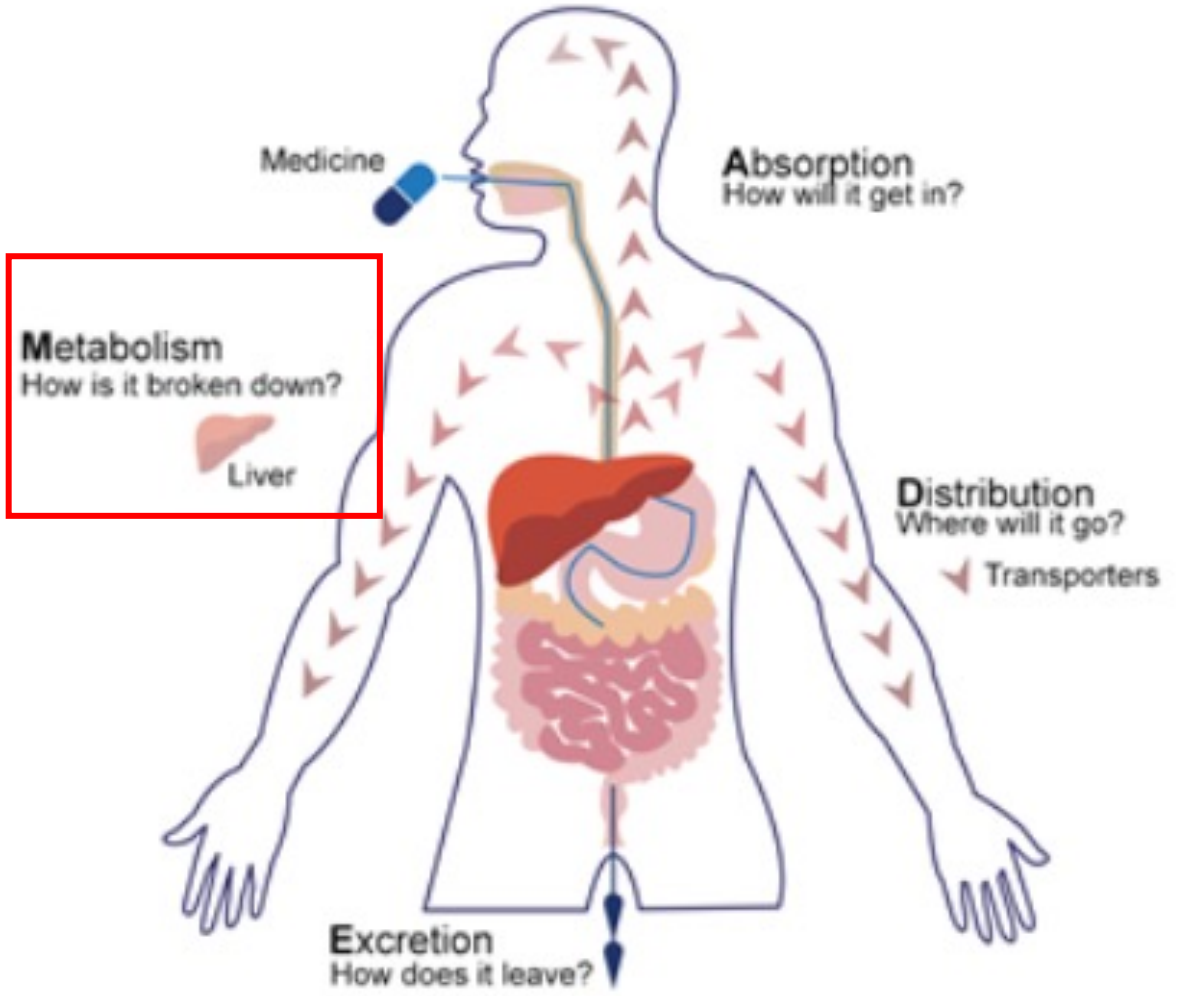


Statins– use OATP1B1 transporter to access the liver.

GWAS – OATP1B1 missense variant. Decreased heaptic uptake.

Q. How would this influence the effect of statins in the body?

Metabolism



Hugely Important!!

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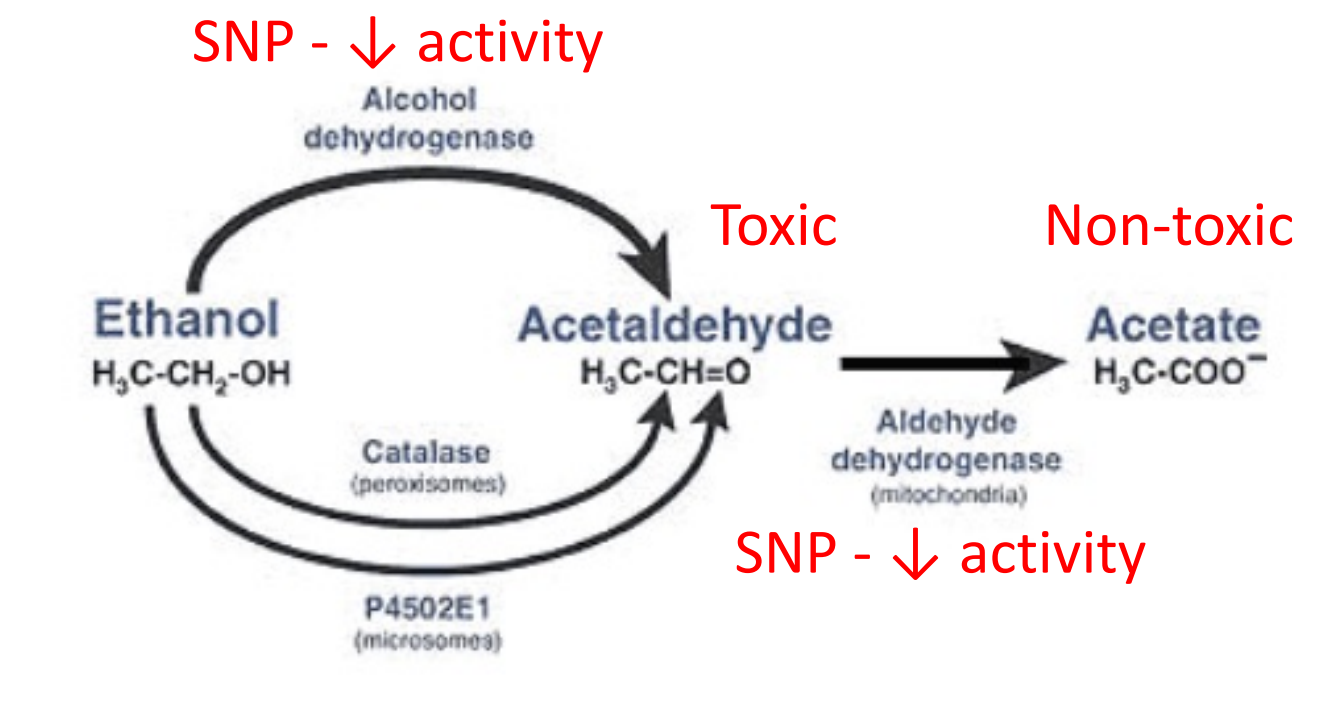
Activation/inactivation (metabolism)

- Drug metabolism – many SNPs identified in drug metabolising enzymes



Alcohol metabolism

Q. What are the different consequence of SNPs in the two alcohol metabolising genes shown opposite?

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Activation/inactivation (metabolism)

- Drug metabolism – many SNPs identified in drug metabolising enzymes

- Some drugs require ‘metabolism’ to become activated – these are prodrugs i.e. initial drug = inactive, metabolised drug = active

A healthy 2-year-old boy went under tonsillectomy and received codeine after discharge from hospital to control pain. The dose was standard for his age and sex and was administered as prescribed. Few days later, he died of the respiratory side effect of codeine. Codeine prodrug converted to morphine

Q. What do you think went wrong?

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Activation/inactivation (metabolism)

- CYP2D6 is involved in metabolism of 20-25% clinically useful drugs (inc codeine)
- Over 100 CYP2D6 allelic variants
- If you carry at two fully active alleles – ultra rapid metaboliser(1-10%)
- If you carry at least one fully active allele – extensive metaboliser (75-85%)
- If you carry at least one reduced function alleles – intermediate metaboliser (10-15%)
- If you carry at two non-functional alleles – poor metaboliser (5-10%)

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Codeine phosphate

Cautions, further information

Variation in metabolism

The capacity to metabolise codeine to morphine can vary considerably between individuals; there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers.

Explain what is meant by complex genetic disease, and outline how we can estimate the heritability of a common complex genetic disease.

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

TO THE EDITOR: Obstructive sleep apnea is not rare in children with hypertrophic tonsils, and the common curative procedure is adenotonsillectomy.[1] Codeine is commonly prescribed for pain after adenotonsillectomy.[2] The respiratory depressant effects of opioids may influence the occurrence of respiratory complications.[3] An estimated one third of cases of apnea in children are not resolved after adenotonsillectomy.[4]

We report on the case of a healthy 2-year-old boy weighing 13 kg, with a history of snoring and sleep-study–confirmed sleep apnea, who underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated, and 6 hours after surgery the boy received 10 mg of meperidine and 12.5 mg of dimenhydrinate intramuscularly and was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup to be administered orally every 4 to 6 hours as needed. On the second evening after surgery, fever and wheezing developed in the child. At 9 a.m. the next day, the child's vital signs were absent, and resuscitation efforts failed.

Postmortem examination showed evidence of chronic tracheitis, aspiration of food particles, and bilateral consolidation in the lungs that was consistent with bronchopneumonia. Codeine (0.70 mg per liter) and morphine (32 ng per milliliter) were detected in the femoral blood by means of gas chromatography–mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the *CYP2D6* allele, resulting in the ultrarapid-metabolizer phenotype.

In this case, the prescribed and administered dose of codeine was within the recommended range of 1 to 3 mg per kilogram of body weight per day.[1,2] Increased conversion of codeine to morphine due to ultrarapid metabolism resulted in toxic accumulation of morphine. The concentration of 32 ng per milliliter of morphine at autopsy exceeded therapeutic levels and may have contributed to respiratory depression and death. Respiratory depression has been shown in young children with serum morphine concentrations exceeding 20 ng per milliliter.[3]

The boy had other contributing factors that should be considered. Autopsy results indicated evidence of bronchopneumonia, further enhancing the risk of hypoxemia. As many as a third of young children with obstructive sleep apnea remain symptomatic after adenotonsillectomy,[4] showing decreased responsiveness to increases in the partial pressure of carbon dioxide.[5] Recurrent episodes of hypoxemia may lead to alterations in the μ-opioid receptor and increased sensitivity to morphine. A child who has recurrent episodes of hypoxemia and who is also an ultrarapid metabolizer of codeine may have a significantly increased risk of respiratory depression. We are unaware of any other fatalities attributable to the ultrarapid metabolism of CYP2D6 in this susceptible population.

Because of the polymorphic nature of codeine metabolism and the fact that adenotonsillectomy does not reverse all cases of obstructive sleep apnea, codeine cannot be considered a safe outpatient analgesic for young children after adenotonsillectomy.

Long way to go!

Genome-wide association studies (GWAS) represent a fairly cost effective and unbiased method for identifying gene–drug interactions and might be particularly important for identifying pharmacodynamic drug–gene interactions and providing novel insights into mechanisms of action or toxicity. However, <10% of the studies in the GWAS catalogue have so far investigated drug response

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Progress Check

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Part 1

- Mendelian diseases are controlled by a single gene and complex diseases are controlled by multiple genes
- Genome-wide association studies analyze association between millions of SNPs throughout the genome with a complex disease
- Detect risk alleles or protection alleles
- Moving into era of whole genome sequencing

Part 2

- Different people respond differently to the effect of medications
- Genetic factors influence the way individuals respond to medication

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