

Genomic and Precision Medicine

Week 4: Methods for Dissecting the
Genetic Basis of Complex Diseases



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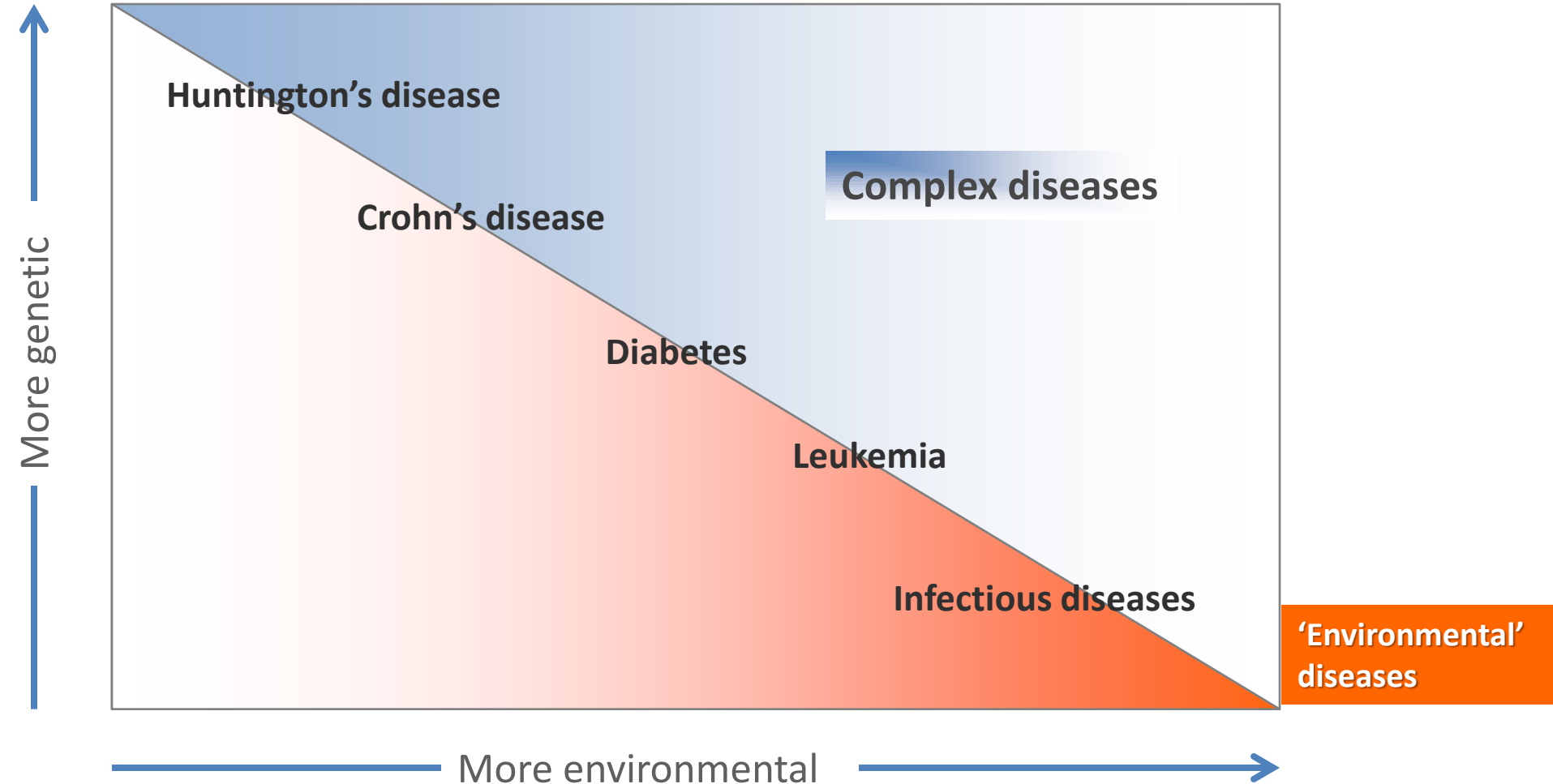
The Lecture

- **MODULE 1:** Background
 - Mendelian vs. complex diseases
 - How do we know a trait has a genetic component
- **MODULE 2:** GWAS methods
 - Genotyping
 - Study designs
 - Confounding and bias
- **MODULE 3:** GWAS analysis
 - Significance testing
- **MODULE 4:** GWAS interpretation
 - Measures of effect
 - External validity
- **MODULE 5:** What do we know about the genetics of common, complex diseases?

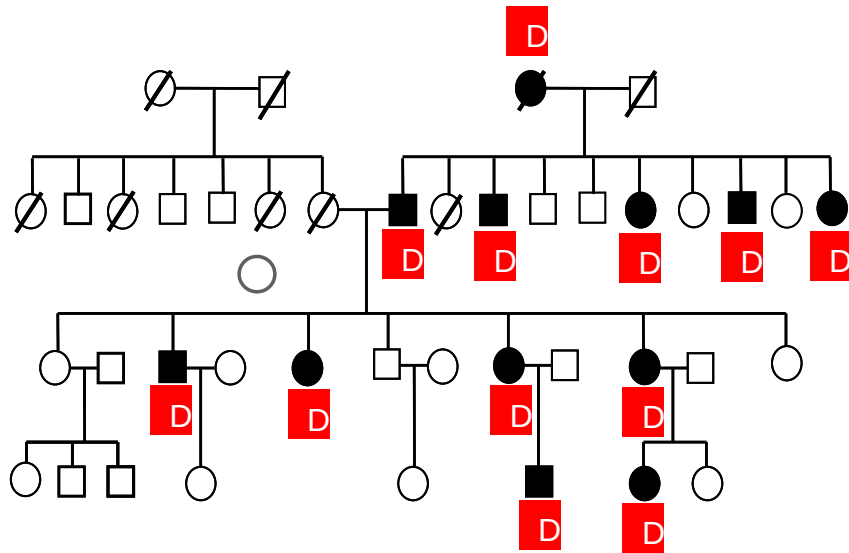
MODULE 1: Background

Spectrum of genetic disease

Mendelian genetic diseases



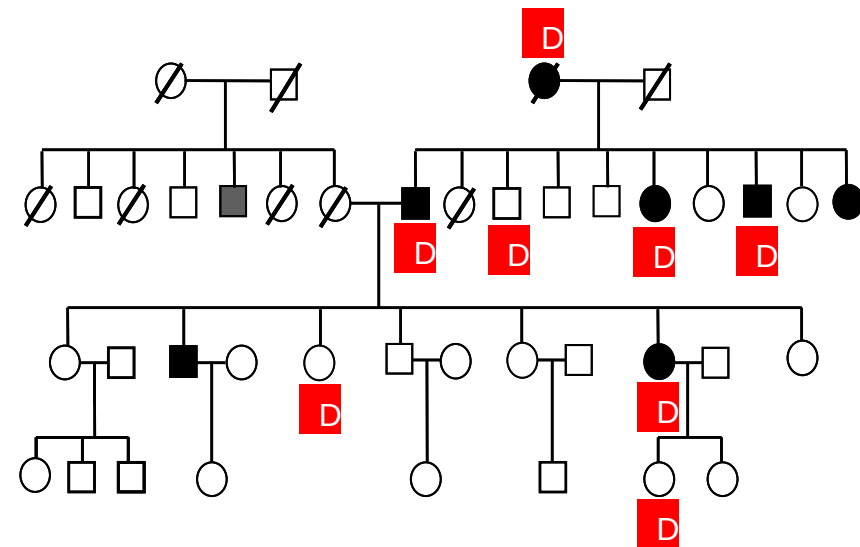
Mendelian vs. complex diseases



Mendelian

Clear inheritance pattern
(dominant, recessive, etc.)

High penetrance

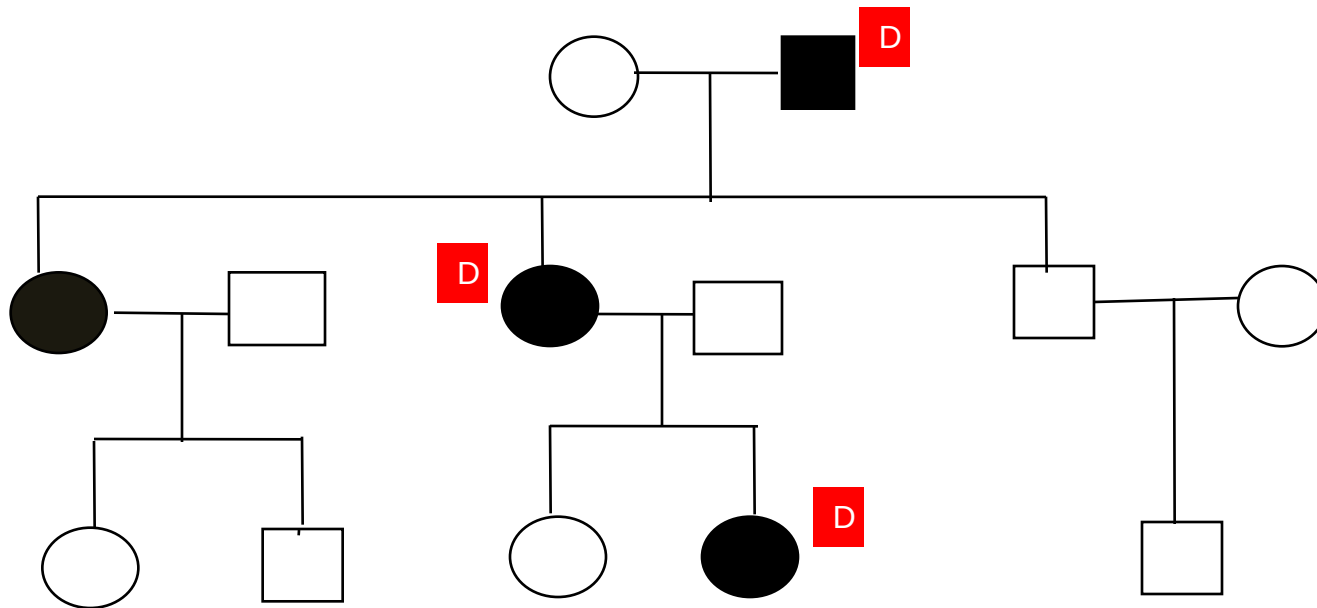


Complex

No clear inheritance pattern
Why????

Phenocopies

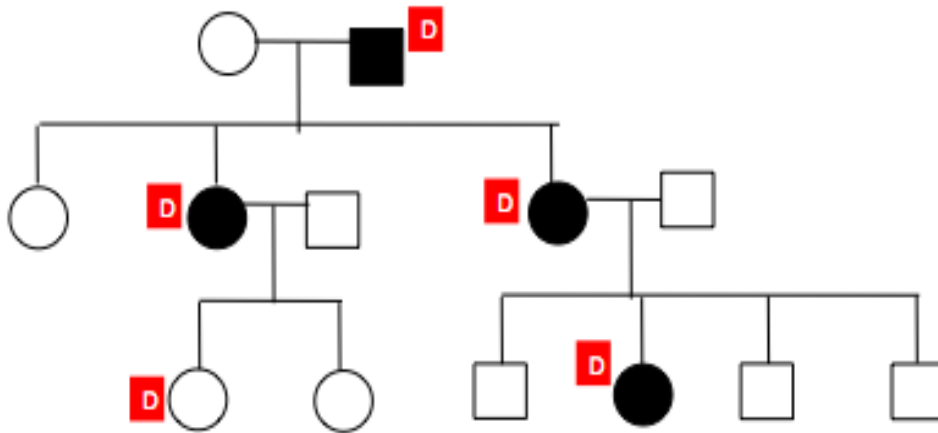
Non-genetic form of disease that is indistinguishable at the clinical level from genetic form of disease



Only 10% of breast cancer is thought to be genetic

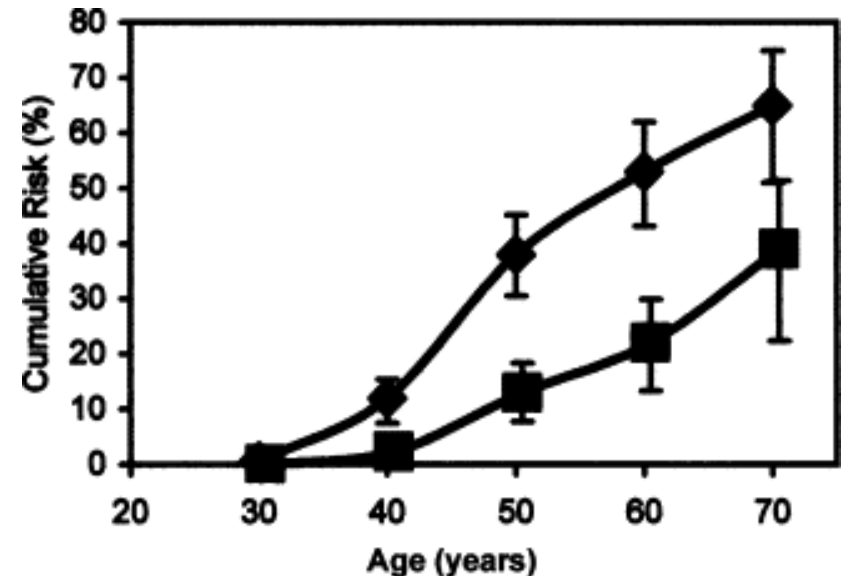
Incomplete penetrance

Not all genetically susceptible people develop disease



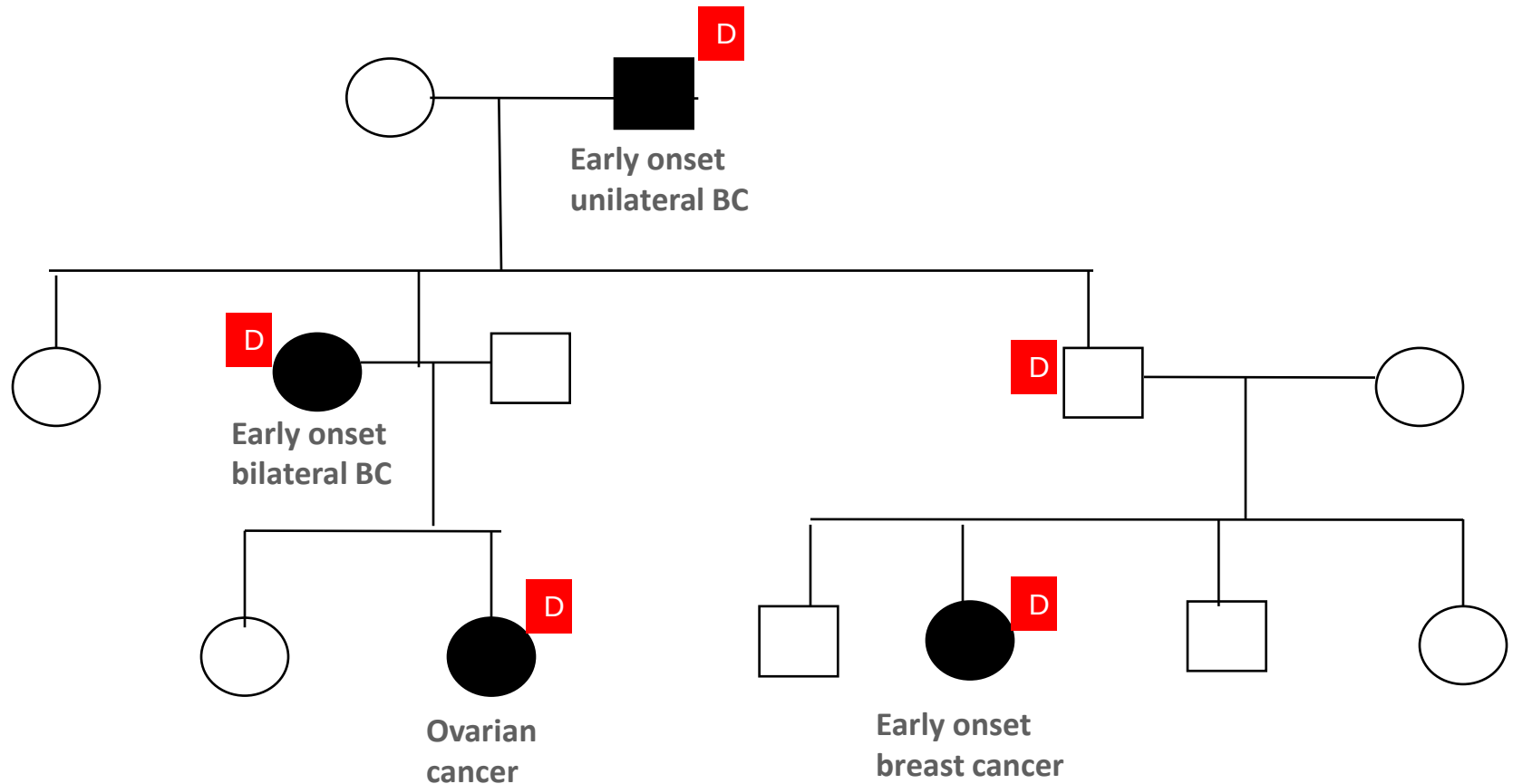
*Penetrance =
Probability of disease
in mutation carriers*

Cumulative risk of breast (♦) and ovarian (▪) cancer in BRCA1-mutation carriers.



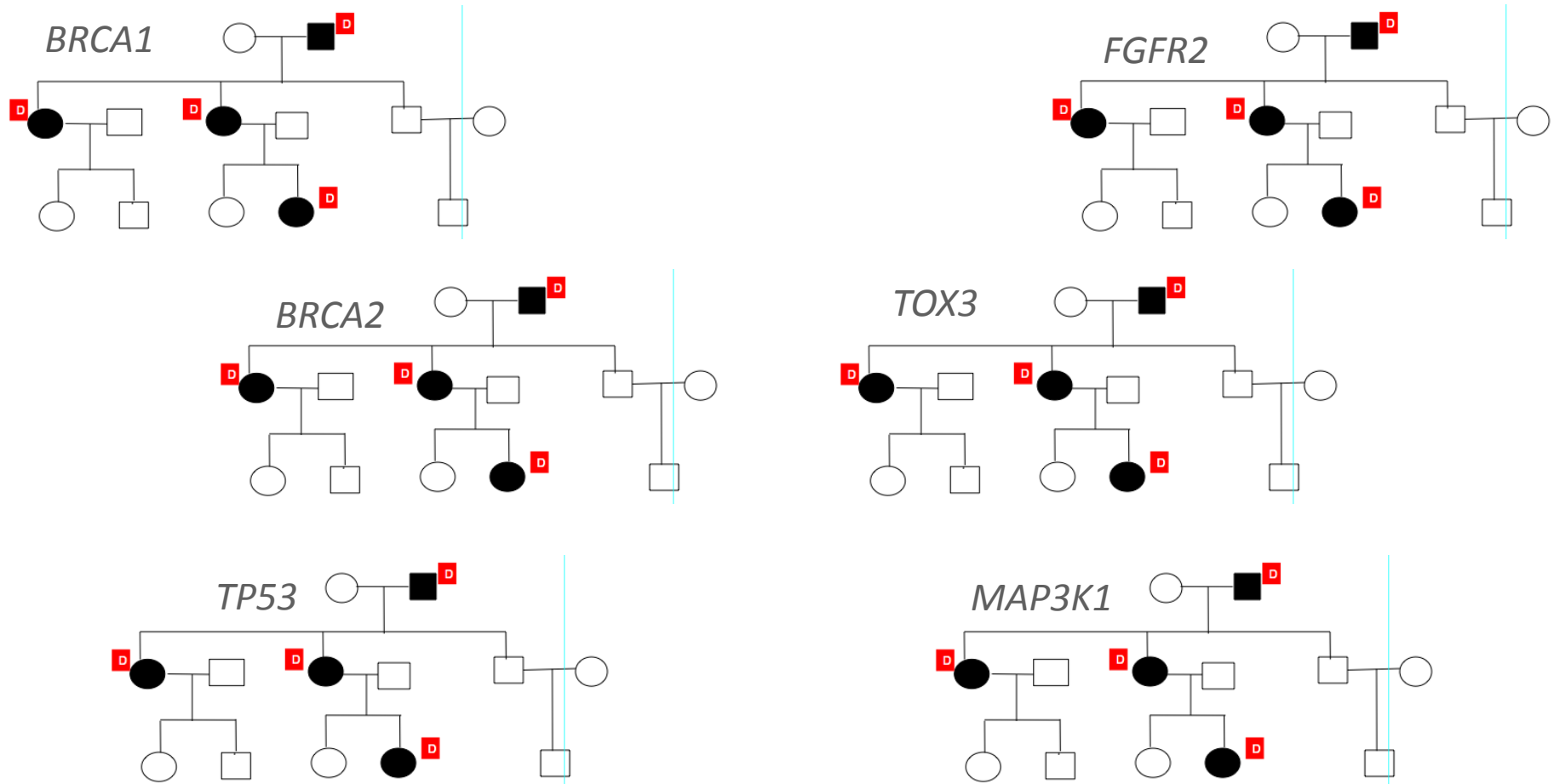
Variable expressivity

Same genetic factor causes multiple phenotypes



Genetic heterogeneity

Mutations in different genes can lead to same disease



Complex vs Mendelian traits

○ Mendelian

- Typically rare diseases (<1% prevalence) with single cause that is genetic
- High penetrance

○ Complex

- Usually common diseases with multiple causes, both genetic and non-genetic
- Low penetrance

Symptoms suggestive of a genetic condition

- Earlier age at onset of disease than expected
- Condition in the less often affected sex
- Family history with multiple generations affected
- Disease in the absence of known risk factors

MI @ 25 yrs



MI @ 80 yrs



Breast Ca in male



Breast Ca in female



Diabetes in lean



Diabetes in obese



Human genetic approaches for finding disease genes

	Candidate gene	Genome-wide
Populations	 Genetic association	 GWAS
Families		 Linkage analysis NGS for rare variants

Question

Which of the following is NOT a characteristic of complex diseases?

- A. Genetic heterogeneity
- B. Mendelian inheritance
- C. Variable expressivity
- D. Reduced penetrance

Answer

B. Mendelian inheritance

Complex traits are characterized by a departure from Mendelian patterns of inheritance