BIOL3120 –Human Genetics and Evolutionary Medicine

Heritability and Polygenic Inheritance

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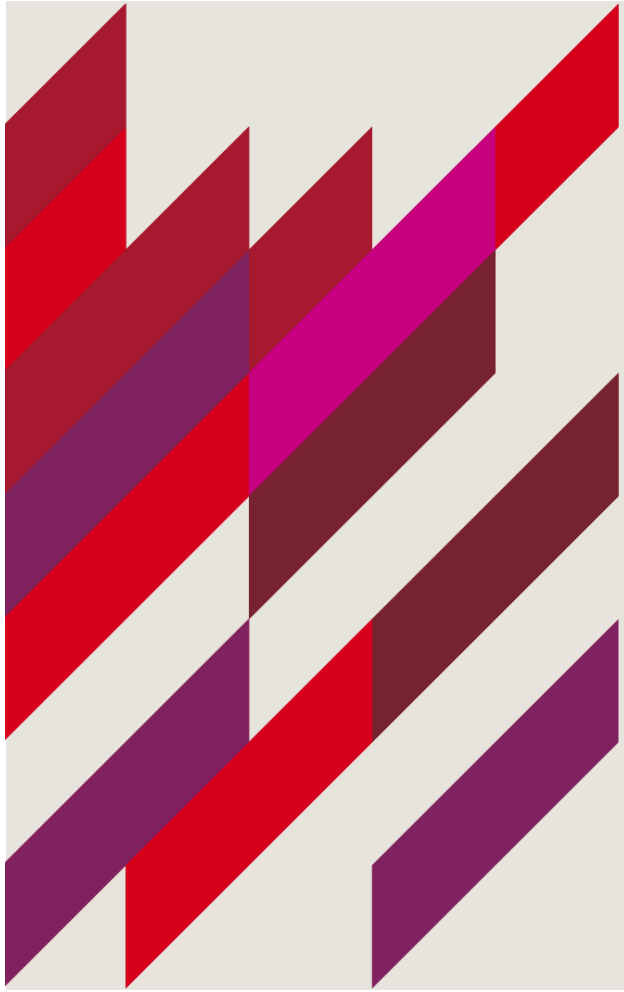
LEARNING OBJECTIVES



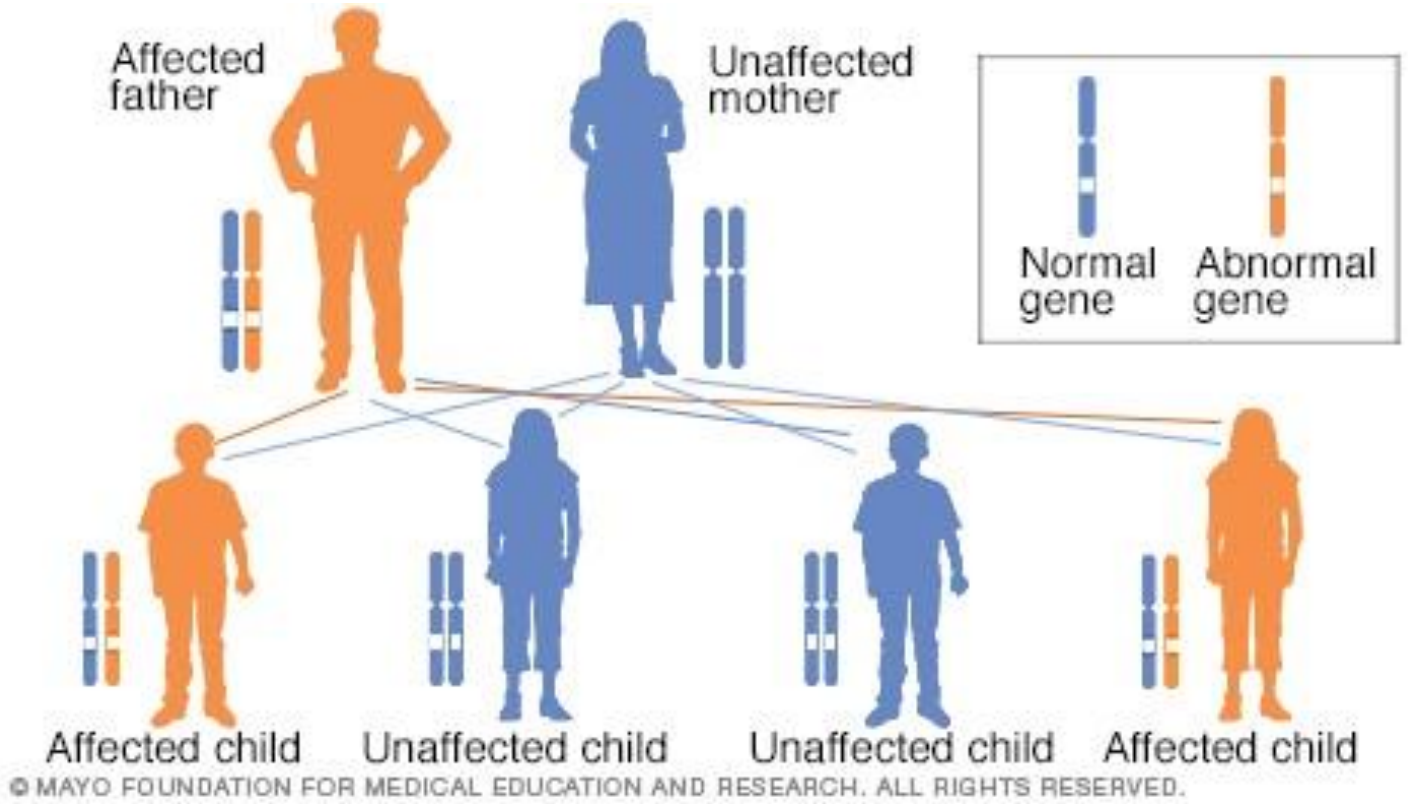
On successful completion of this lecture, you will be able to:

- Discuss factors that indicate a possible genetic basis for a condition
- Define heritability & understand it's limitations
- Discuss polygenic inheritance and polygenic risk scores

Terms

- Monogenic inheritance
  - Caused by variation in a single gene
  - Striking familial inheritance patterns
  - Sickle cell anaemia, cystic fibrosis, Huntington disease, Duchenne muscular dystrophy
- Polygenic inheritance
  - Caused by the combined action of more than one gene
  - Hypertension, coronary heart disease, diabetes
- Environmental factors
  - Complex diseases occur as a result of many genomic variants, paired with environmental influences

Monogenic inheritance

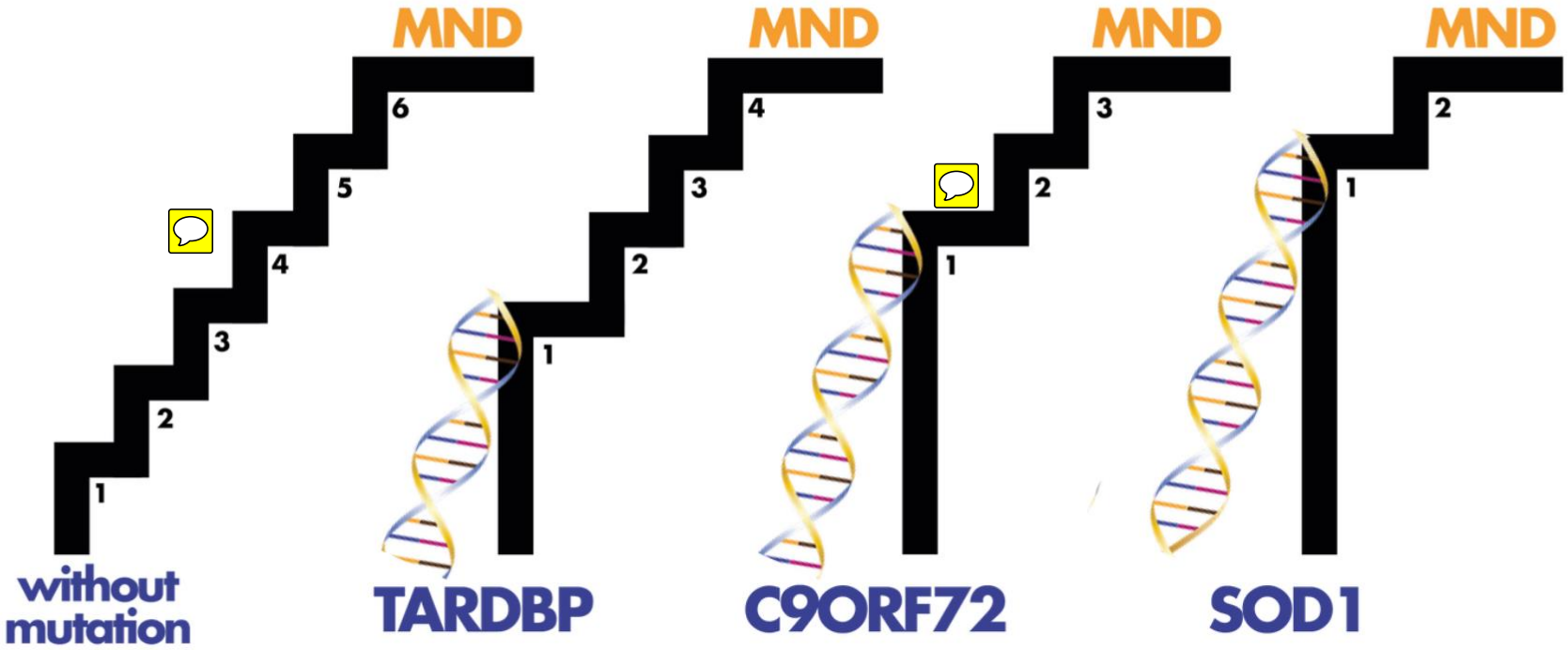


Polygenic inheritance

Human height.
There is great variation in human height between different individuals.
Jane Ades/National Human Genome Research Institute.

Complex disorders

Genetic and environmental **risk factors**



CAUSES AND DISEASE MECHANISMS / MND RESEARCH

Steps to understanding MND

AUGUST 3, 2018 NICKJAMESCOLE 2 COMMENTS

THE OFFICIAL BLOG OF THE mnda motor neurone disease association

Al-Chalbi *et al* Lancet Neurol; 13: 1108–13, 2014
Chio et al Neurology :e1-e8, 2018

How to tell how ‘genetic’ a disease is: Relative risk ratio

$$\lambda_r = \frac{\text{Prevalence of the disease in the relatives of an affected person}}{\text{Prevalence of the disease in the general population}}$$

TABLE 8-2 Risk Ratios λ_s for Siblings of Probands with Diseases with Familial Aggregation and Complex Inheritance

Disease	Relationship	λ_s
Schizophrenia	Siblings	12
Autism	Siblings	150
Manic-depressive (bipolar) disorder	Siblings	7
Type 1 diabetes mellitus	Siblings	35
Crohn disease	Siblings	25
Multiple sclerosis	Siblings	24

Value of 1 = no more likely to develop condition if you have an affected relative

Value higher than 1 = relative of affected person more likely to develop the condition

How to tell how ‘genetic’ a disease is: Family history case-controlled studies

- Multiple sclerosis (MS) study example: 3.5% of first-degree relatives of people with MS also had MS themselves.
- Compared to 0.2% of first-degree relatives of people without MS
- 3.5 / 0.2 = 17.5
- The odds of having a first degree relative with MS were 17.5x higher amongst MS patients than controls.
- Suggests genetic factors underlying

Problem:

- People who are related tend to have environmental factors in common.

- How do we tease apart genetic vs. environmental influences?

Heritability

- Define heritability & understand it's limitations

What is Heritability?

- A measure of how well differences in people's genes account for differences in their traits
  - Popularly referred to as 'nature versus nurture' debate

- Heritability is a statistical concept that describes how much of the variation in a given trait can be attributed to genetic variation

- Used in reference to the resemblance between parents and their offspring. In this context, high heritability implies a strong resemblance between parents and offspring with regard to a specific trait, while low heritability implies a low level of resemblance.

- An estimate of the heritability of a trait is specific to one population in one environment, and it can change over time as circumstances change.

What is Heritability?

- Heritability estimates range from zero to one.

- A heritability close to one indicates that almost all of the variability in a trait comes from genetic differences, with very little contribution from environmental factors.
  - Many disorders that are caused by mutations in single genes, such as phenylketonuria (PKU), have high heritability

- A heritability close to zero indicates that almost all of the variability in a trait among people is due to environmental factors, with very little influence from genetic differences.
  - Characteristics such as religion, language spoken, and political preference have a heritability of zero because they are not under genetic control.

- Most complex traits in people, such as multifactorial diseases, have a heritability somewhere in the middle, suggesting that their variability is due to a combination of genetic and environmental factors.

Heritability limitations

- Heritability does not indicate what proportion of a trait is determined by genes and what proportion is determined by environment.
  - a heritability of 0.7 does not mean that a trait is 70% caused by genetic factors; it means than 70% of the variability in the trait in a population is due to genetic differences among people.

- Heritability does not determine which genes/loci are involved in the trait/disease.

- Estimating Trait Heritability


Heritability
Khan Academy

Polygenic Inheritance

- Discuss polygenic inheritance and polygenic risk scores

Polygenic inheritance

- Caused by the combined action of more than one gene
  - Height, skin colour
  - Hypertension, coronary heart disease, diabetes
- The inheritance of polygenic traits does not show the phenotypic ratios characteristic of Mendelian inheritance, though each of the genes contributing to the trait is inherited as described by Gregor Mendel.

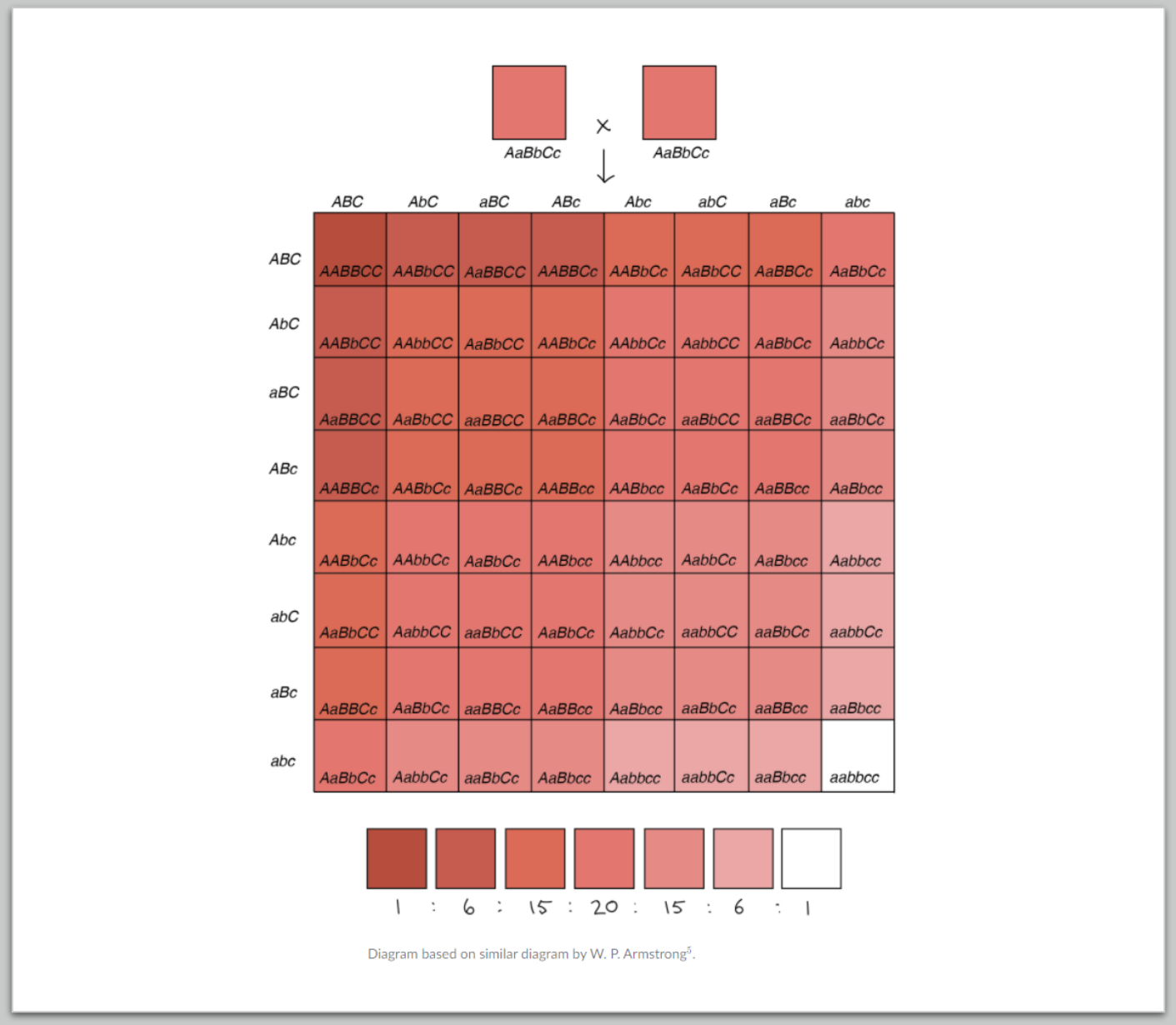


Diagram based on similar diagram by W. P. Armstrong[3].

Genetic susceptibility to complex disease

- **Complex disease**: Most medical problems such as heart disease, diabetes, obesity, Alzheimer's disease, asthma, Parkinson's disease, multiple sclerosis, osteoporosis, and sporadic MND, do not have a single genetic cause—they are likely associated with the effects of **multiple genes** in combination with **lifestyle and environmental factors**. These are called complex or multifactorial disorders.

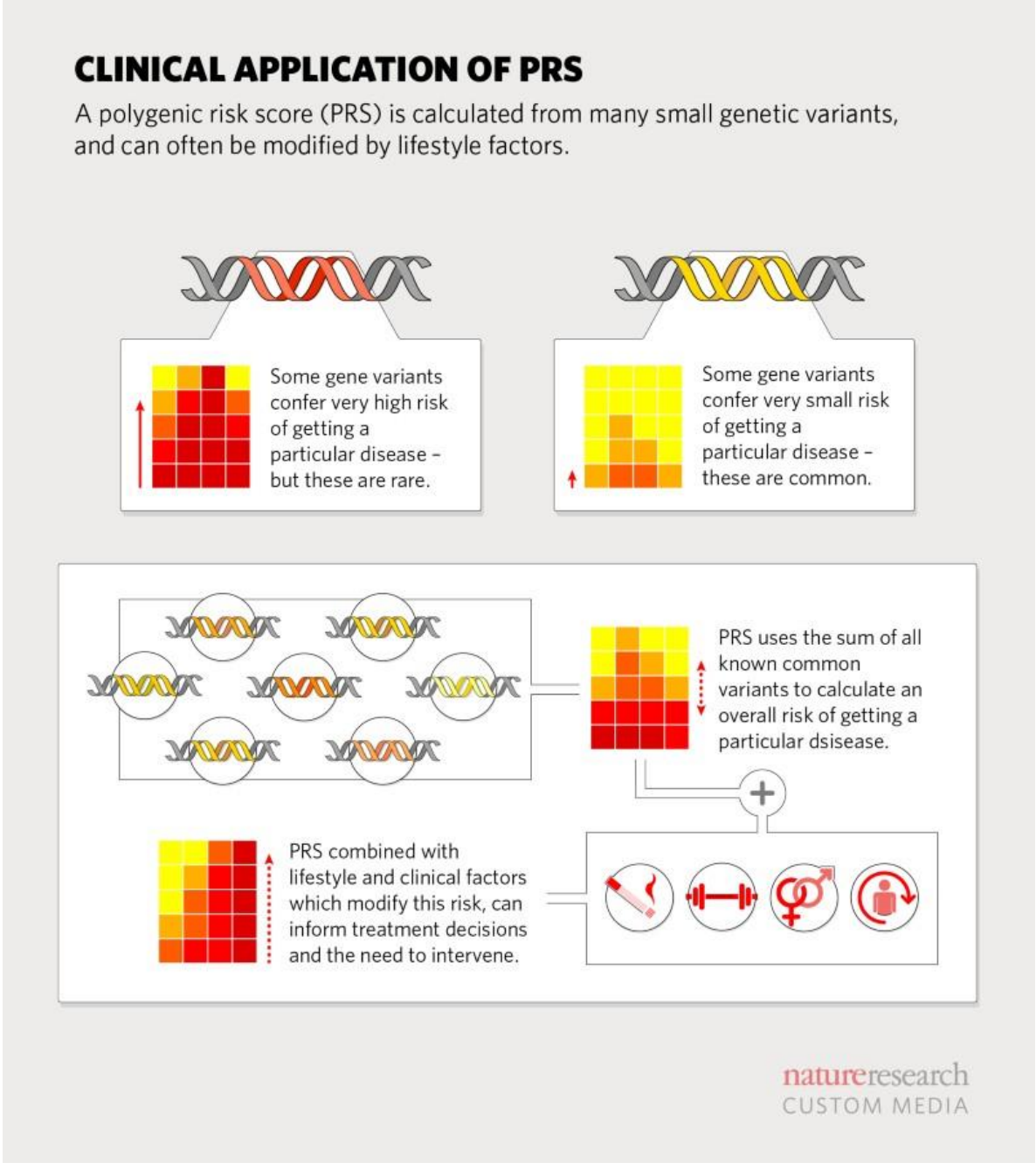
- **Susceptibility (risk) alleles**: an allele, usually inherited, that increases the likelihood of developing a complex disease. The combination of multiple susceptibility alleles and environmental factors may be additive or synergistic, leading to disease.

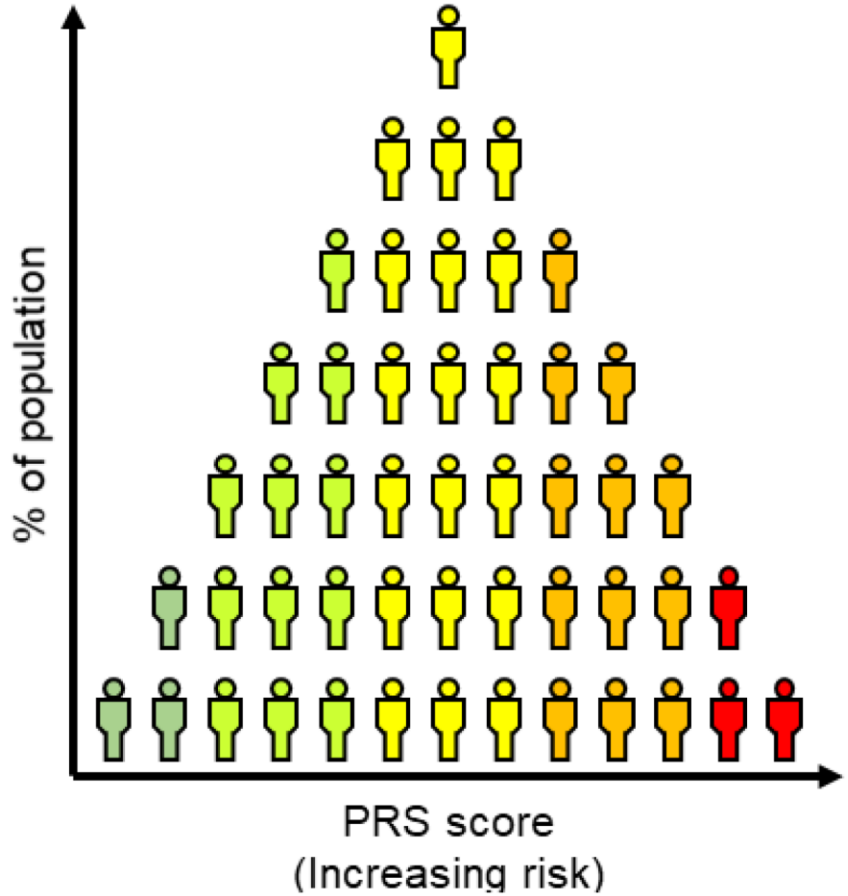
- On their own, they are neither necessary nor sufficient to cause disease

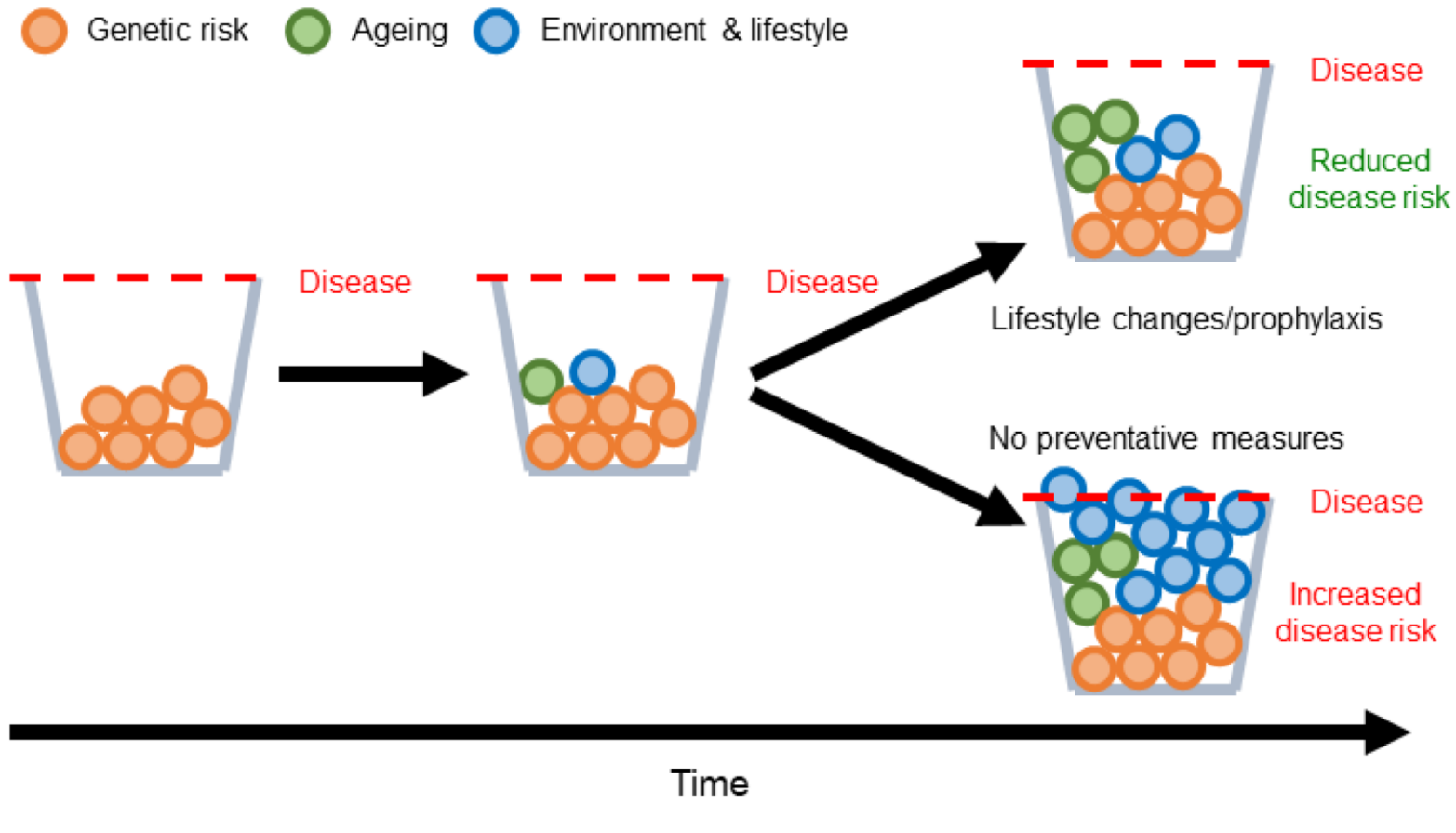
Polygenic Risk Score

- “a substitution of a single nucleotide that occurs at a specific position in the genome, where each variation is present to some appreciable degree within a population (e.g. > 1%)” (Wikipedia)

- 4-5 million per person ~ every 1,000bp on average







Hall A, Bandres-Ciga S, Diez-Fairen M, Quinn JP, Billingsley KJ. Genetic Risk Profiling in Parkinson's Disease and Utilizing Genetics to Gain Insight into Disease-Related Biological Pathways. *International Journal of Molecular Sciences*. 2020; 21(19):7332. https://doi.org/10.3390/ijms21197332

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