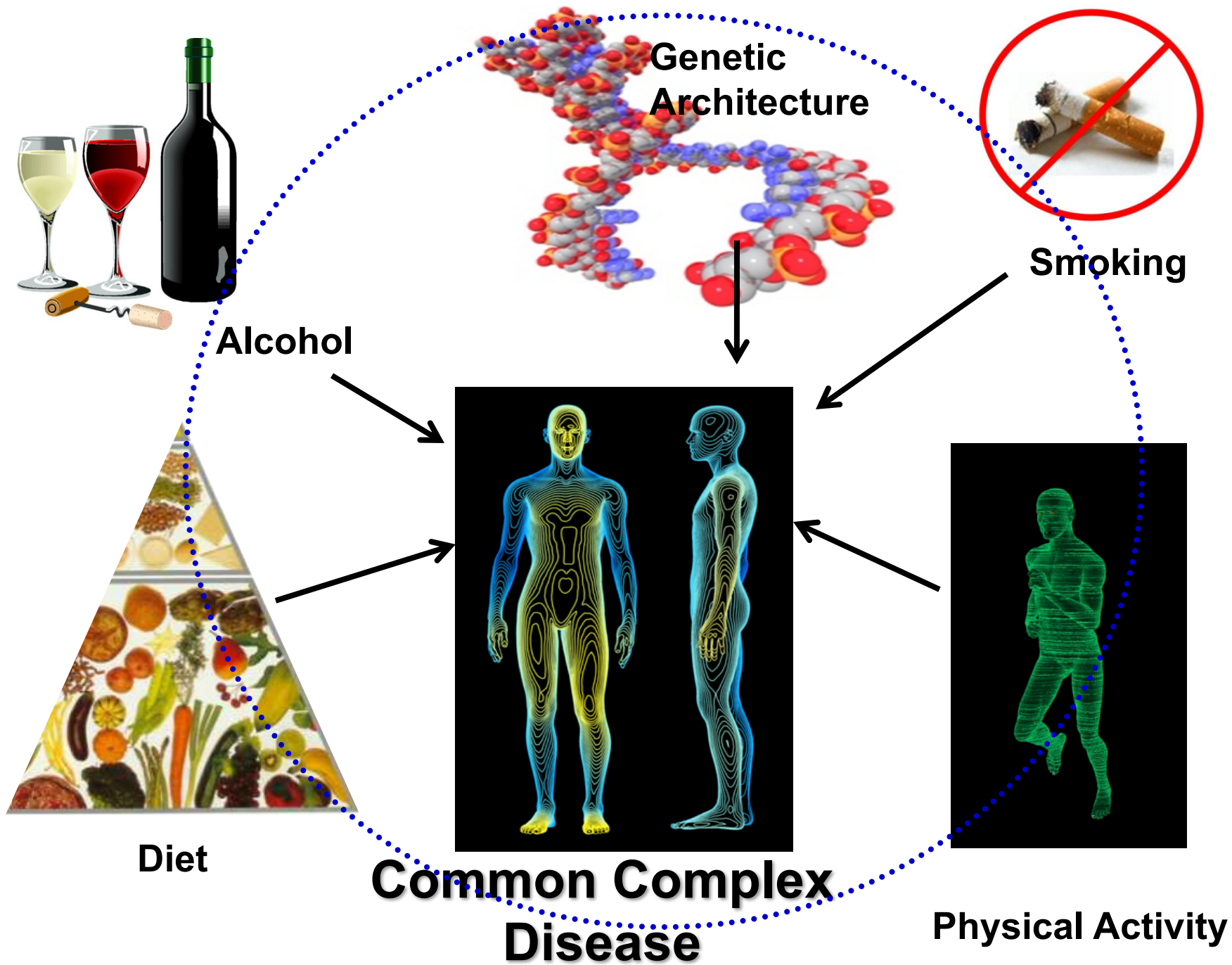


2017_SISG_12_12
Gene-Environment
Interaction

“Almost all human diseases result from gene-environment interaction. Proving, documenting, and quantifying this statement is a long-sought goal of the scientific community and one that, if achieved, could provide fundamental insights into the causes, courses, and prevention of many conditions.”



How Do We Quantify Gene – Environment Interaction?

What is Gene-Environment Interaction?

- **Definition: Distinct effects of an environmental factor in individuals with different genotypes**
- **Examples: Individuals with different genotypes differ in their**
 - **susceptibility to the health effects of exposures such as smoking, drinking, not exercising, etc.**
 - **responses to life events such as trauma**
 - **responses to medications (pharmacogenomics)**

Statistical Definitions of Interaction

Model	Interpretation
No interaction	The same effect of the exposure in people with different genotypes
Synergistic interaction	Greater effect of the exposure in people with a genotype of interest than in people with other genotypes
Antagonistic interaction	Smaller effect of the exposure in people with a genotype of interest than in people with other genotypes

Gene-Environment Interaction

Strata	Cases	Controls
G+E+	a	b
G+E-	c	d
G-E+	e	f
G-E-	g	h

Odds Ratio (OR)

ah / bg

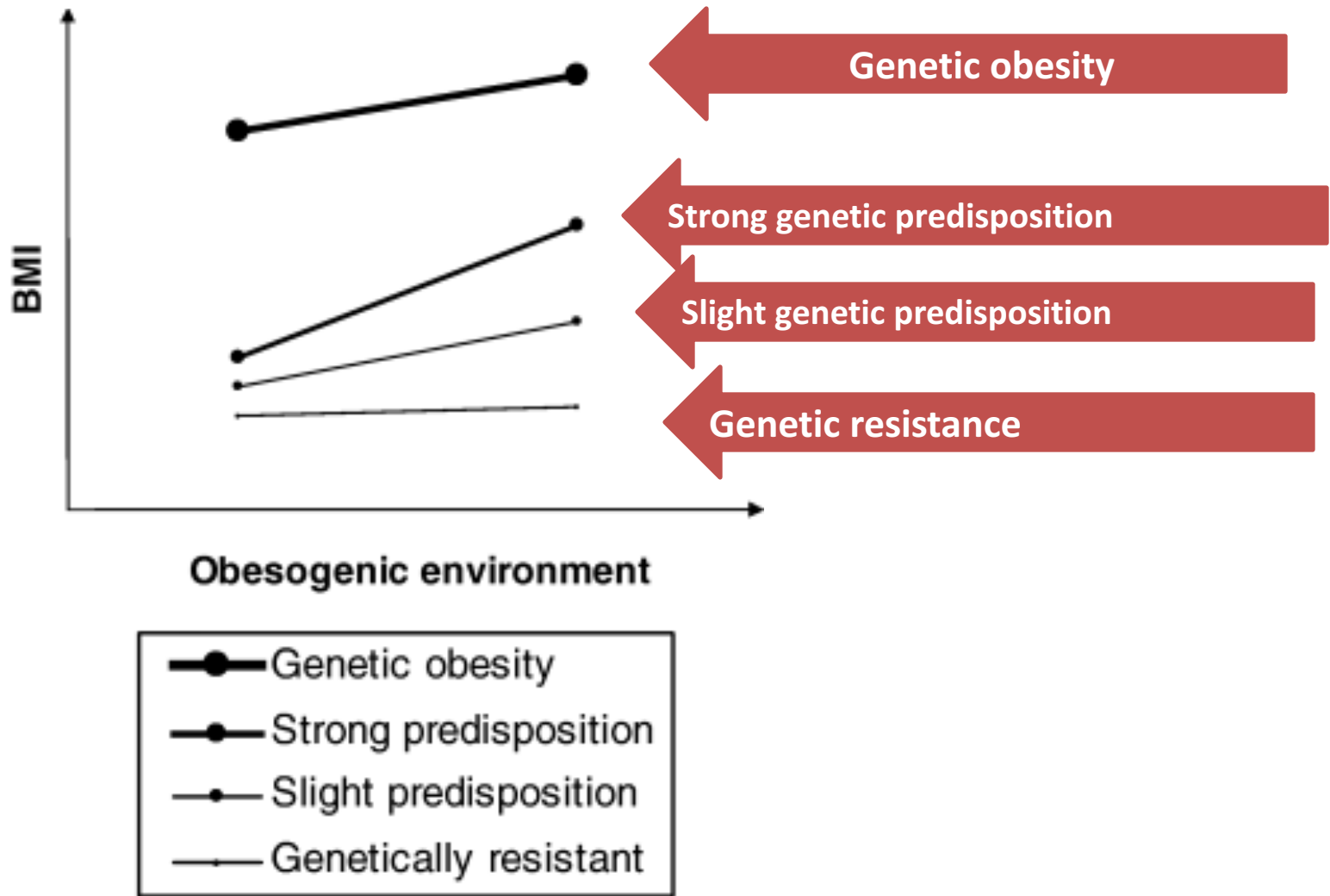
ch / dg

eh / fg

1

- $OR_{\text{Interaction}} = OR_{G+E+} / OR_{G+E-} \cdot OR_{G-E+}$
- If $OR_{\text{Interaction}} \geq 1$, multiplicative effects

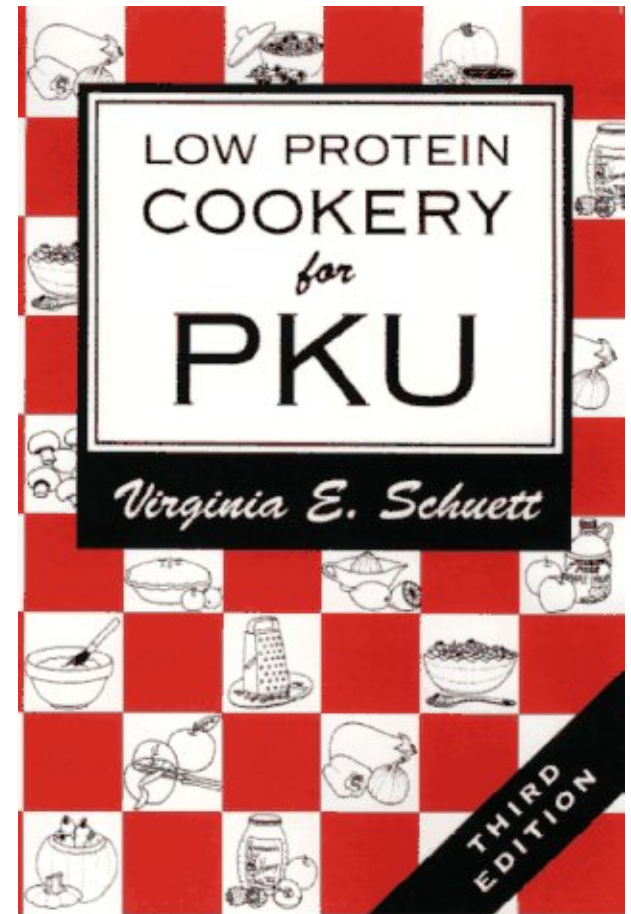
Four levels of genetic susceptibility to obesity relative to differences in obesogenic conditions:



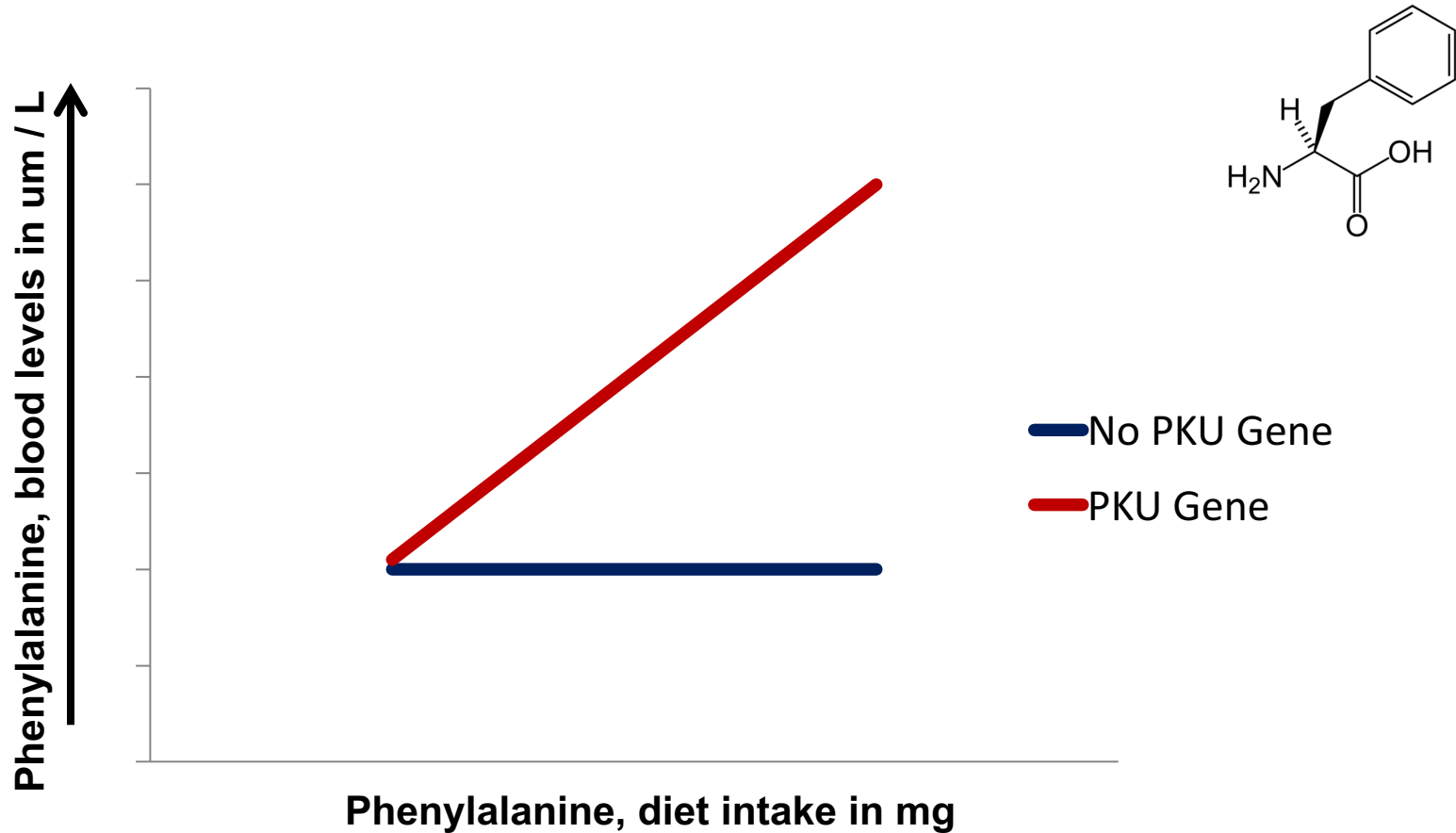
(From Loos and Bouchard, 2003; ref 10, reproduced with permission.)

Classic G-E Interaction Examples: Phenylketonuria (PKU)

- Rare (1/10,000 newborns) condition where infant cannot metabolize the amino acid called phenylalanine.
- Autosomal recessive
- If untreated, it can cause problems with brain development, leading to progressive, brain damage, and seizures.

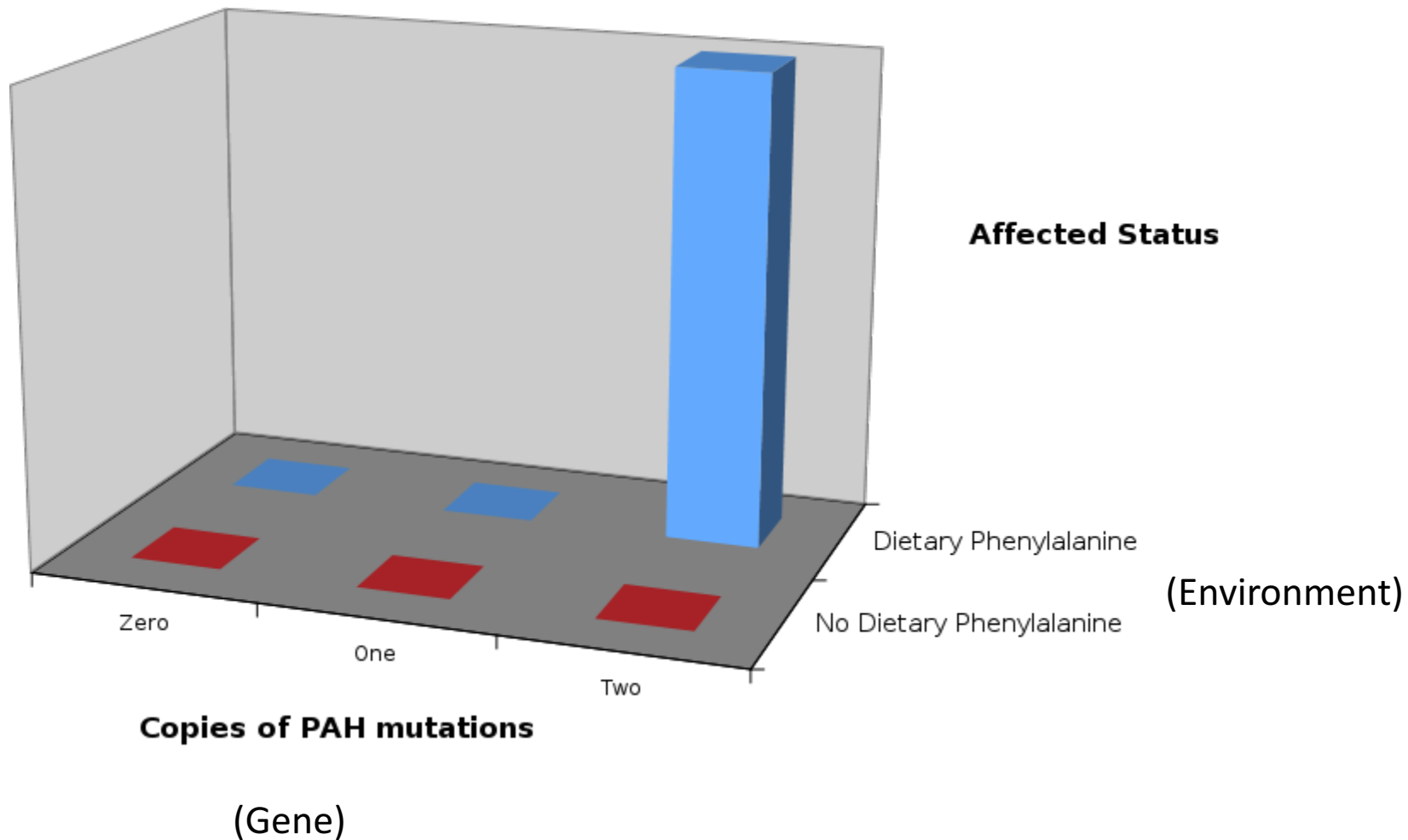


G-E Interaction: Phenylketonuria (PKU)



Only individuals with recessive mutations in the causative gene – **phenylalanine hydroxylase** – that are exposed to phenylalanine in the diet are susceptible to PKU.

Gene-Environment Interaction Example – Phenylketoneuria (PKU)



How do we Quantify G-E Interaction ?

- **Studies of interaction need to consider the scale of measurement**
- **Additive scale more consistent with biological models**
- **Methods development needed to make tests on additive scale more accessible**
- **Large sample sizes needed, so collaboration is essential**

Gene-environment interaction: The process

- **Phenotype**
 - How do we define it?
 - Do we have reason to think it's genetically controlled?
 - Is it likely to have effects mediated by a given environmental factor?
- **Genotype**
 - Evidence for linkage, association, interaction?
 - Where are the SNPs (promoter, intron, exon)?
 - What is the SNP?
 - How discovered, how validated?
 - Frequencies in population (including your study sample)