

# EPIGENETICS



## THE CODE

The genetic code is the sequencing of certain molecules (nitrogenous bases) where every grouping of three (3) bases (codons) code for one amino acid. Codons strung together make up genes, which tell the cell how to build a protein. The full set of DNA is the complete instructional manual to make all proteins.

- Nitrogenous bases comprising the “code”:
  - A (Adenine) 
  - T (Thymine) 
  - C (Cytosine) 
  - G (Guanine) 

Your “**genotype**” is the code that makes all proteins. Your “**phenotype**” is what is expressed from the code; in other words, it is the protein created from the code. Not all protein is expressed. The control of the expression is regulated by epigenetic factors.

## COOL FACTS

**Genotype:** Nucleotide difference between humans and chimpanzees is surprisingly small (1-2% difference)

**Phenotype:** Eighty (80%) of the proteins are different between the two species!

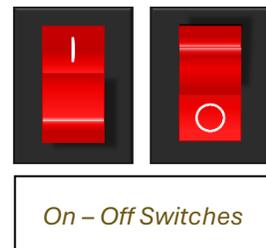
- Over 3 billion base pairs in the code
- 20,000 genes
- Greater than 400,000 proteins

## EPIGENETICS

Epigenetic regulation involves modifications to DNA and histones that ***influence gene expression without altering the genetic code.***

Regulation encompasses DNA methylation, histone acetylation, and other posttranslational modifications that modulate accessibility and transcriptional activity.

- **Methylation** = adding a methyl group ( $\text{CH}_3$ )
- **Acetylation** = adding an acetyl group ( $\text{CH}_3\text{CO}$ )
- **Phosphorylation** = adding a phosphate group ( $\text{PO}_4$ )



# EPIGENETICS



## METHYLATION

Methyl groups can be added to cytosine units within the DNA code. If a series of three cytosines is methylated, the gene is not expressed (we don't read that gene and its protein is not produced)

- **DNA Methyltransferases** = enzymes adding the methyl groups
- **SAM**: S-adenosyl methionine = a molecule used to donate methyl groups
- **Folic Acid** and **Cobalamin** are vitamins that help transfer methyl groups
- **Methionine, Cysteine, and Homocysteine** are amino acids that help transfer methyl groups



## IMPAIRED METHYLATION

**Polymorphism**: A change in the DNA sequence that occurs in **at least 1%** of a given population. If it's rarer than that, it's usually called a **mutation**.

- **SNP (Single Nucleotide Polymorphism)** one "letter" (base) in the DNA code is different (A → G).
- **Insertion/deletion polymorphisms** — extra or missing DNA bases.
- **Variable number tandem repeats (VNTRs)** — repeated DNA sequences in different lengths.

### Example of an SNP

#### **MTHFR (Methylenetetrahydrofolate reductase) C677T**

- **Location**: The "C677T" label refers to position 677 in the gene's DNA sequence.
- **What changes**: At that position, the normal DNA base C (cytosine) is replaced by T (thymine).
- **Effect on protein**: This substitution changes one amino acid in the enzyme (alanine → valine). This makes the enzyme less stable and less effective,
- **Functional impact**: People with one copy (heterozygous): ~35% reduction in enzyme activity.  
People with two copies (homozygous): up to ~70% reduction in activity.
- **Why it matters**:
  - Less MTHFR activity → less methylfolate → decreased SAM → less DNA methylation
  - **Higher homocysteine levels (inflammatory)**

#### **NOTE: Genetic Testing**

*Tests assess the DNA code for alterations (polymorphisms or mutations). Some strategies (taking methylated folate/cobalamin) can help. Sometimes there are no fixes for code alterations.*

## ACETYLATION

Acetyl groups can be added to histone protein associated with DNA. If an acetyl group is added, the gene is expressed (we read that gene - the protein is produced)

- **Histone Acetylases (HATs) acetylate lysine residues on histones**, reducing histone–DNA binding, opening chromatin, and **promoting gene transcription**.



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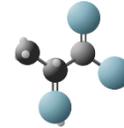


- **Histone Deacetylases (HDACs)** work by **removing acetyl groups** from histones, tightening DNA-histone interactions, making chromatin more compact, **repressing gene expression**.

## Example of an acetylation/deacetylation

### Beta Hydroxybutyrate (ketone body)

- **BHB inhibits histone deacetylases**
- Cells increase production of proteins for antioxidant defense
  - Superoxide Dismutase, catalase, metalloproteinases.
- Cells increase production of proteins for neuroprotection
  - BDNF (Brain-Derived Neurotrophic Factor)
- Cells increase production of proteins for combating inflammation
  - IL-10 increase
  - NFKB decrease



### Fructose (fructose metabolism increases acetyl groups and biases histones toward acetylation)

- Fructose metabolism increases nuclear acetyl-CoA and depletes ATP (higher NADH/NAD ratio)
- Cells make more fat producing enzymes (Acetyl-CoA Carboxylase, Fatty Acid Synthase)
- Cells make more carbohydrate synthesizing enzymes and transporters
- Cells increase production of inflammatory proteins (TNF $\alpha$ , IL-6)



## SLEEP AND MEAL TIMING

You have central and peripheral clocks that governing the expression of proteins. Your central clock is positively or negatively affected by the timing and amount of sunlight, exercise, and food.

- Suprachiasmatic Nucleus receives signals (e.g., daylight); communicates with peripheral clocks via the autonomic nervous and endocrine (cortisol – melatonin) systems.

### MEAL TIMING

- **Early Breakfast**
  - Activates gene transcription of PER and CRY and subsequent processes
  - More GLP1 secretion
  - Improved insulin sensitivity
  - More responsive Beta cells
  - Higher GLUT4 activity
  - Increased transcription of glycogen synthase
- **Late-night eating**
  - Activates gene transcription for adipogenesis
  - Prolonged elevation of glucose
  - Increased hunger upon waking
  - Decreased serum leptin
  - Down regulation of MAPK pathway and autophagy





# EPIGENETICS

The concept of what creates wellness is easy. The effort/sacrifice needed to achieve it is challenging. Choices to enhance lean mass and aerobic capacity while decreasing visceral adiposity are incredibly important for longevity and quality of life.

- “**Sarcopenia** is associated with a significantly higher risk of mortality, independent of population and sarcopenia definition”
  - Xu, J., Wan, C.S., Ktoris, K., Reijnierse, E.M. and Maier, A.B., 2022. Sarcopenia is associated with mortality in adults: a systematic review and meta-analysis. *Gerontology*, 68(4), pp.361-376.
- **Cardiorespiratory** Fitness RF was significantly related to longevity over the course of 4 decades in middle-aged, employed men free of CVD. The benefits of higher midlife CRF extend well into the later part of life. Each unit increase in  $VO^2_{max}$  was associated with a **45-day increase in longevity**.
  - Clausen, J.S., et al., 2018. Midlife cardiorespiratory fitness and the long-term risk of mortality: 46 years of follow-up. *Journal of the American College of Cardiology*, 72(9), pp.987-995.
- In this nationwide cohort study, **higher visceral adiposity** was significantly associated with an increased risk of premature mortality and reduced life expectancy at age 40 among US adults.
  - Xue, M., Zhang, X., Chen, K., Zheng, F., Wang, B., Lin, Q., Zhang, Z., Dong, X. and Niu, W., 2025. Visceral adiposity index, premature mortality, and life expectancy in US adults. *Lipids in Health and Disease*, 24(1), p.139.

## ENZYME LONGEVITY

**Metabolic enzymes that determine *direction* or *commitment* turn over faster** than enzymes that simply keep reactions possible or function as structure.

PROTEIN	FUNCTION	HALF-LIFE
Glucokinase	Carbohydrate Metabolism	8-24 hours
Glycogen Synthase	Carbohydrate Metabolism	8-24 hours
PFK (Phosphofructokinase)	Carbohydrate Metabolism	2 hours
Pyruvate Kinase	Carbohydrate Metabolism	24hours
ACC (Acetyl CoA Carboxylase)	Fat Synthesis	1-3 days
FAS (Fatty Acid Synthase)	Fat Synthesis	1-2 days
CPT-1	Fat Burning	1 day
Citrate Synthase	Krebs Cycle	5-10 days
Myosin	Muscle Structure	7-21 days

**Hepatic metabolic enzyme profile:** Measurable change within **3–5 days** (not just enzyme *activity*).  
*A five-day low carbohydrate diet significantly changes metabolic enzyme expression and count.*

*Your choices largely determine the expression of the DNA code.*

