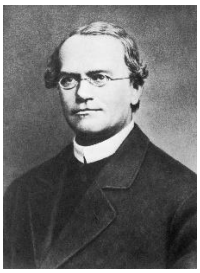
Mendel, the Chromosomal Theory of Inheritance, and DNA As the Hereditary Material

Why Do We Sequence Nucleic Acids??

- **Dumb question???**
  - Yes, because we all know that nucleic acids control phenotype.
    - Well we have not known that forever.
  - So how did we learn this?

Three lines of evidence converged that lead to this discovery

- Phenotypes are controlled by genes
- Genes are located on chromosomes
- Chromosomes are made up of DNA (one of the nucleic acids).



Gregor Mendel

Dramatically changed our perception of heredity

- Particulate factor concept
  - ***Some physical factor existed that controlled phenotype***

Traits have a dominant and recessive forms

- Proof
  - F_1 generation
    - Dominant form appears
    - Recessive form disappears
- F_2
  - Recessive form reappears

Some factor is not lost; points to a physical entity

Mendel's 1st Law, the Law of Segregation

- A single form of the factor controlling phenotype was passed to the gamete during reproduction.
  - Event occurs during reduction step of meiosis
- One of two forms of the factor was passed through the gamete to the offspring.
  - Proof??
    - F_2
      - 3:1 ratio in F2 generation segregating for one trait
        - 3/4 dominant form
        - 1/4 recessive form

Again more evidence a factor is involved

	A	a
A	AA	Aa
a	Aa	aa

    - F_3 generation
      - Offspring of recessive F_2 plants all recessive form
      - Some offspring of F_2 dominant form plants all dominant form
      - Some offspring of F_2 dominant form plants produce 3:1 dominant to recessive forms
      - Ratio of dominant form F_2 plants in F_3 generation
        - 2/3 segregate for dominant and recessive forms in 3:1 ratio
        - 1/3 all dominant F_3 plants

Mendel's 2nd Law, the Law of Independent Assortment

- Each trait was controlled by a unique factor
- Proof??
    - 9:3:3:1 ratio in the F2 generation segregating for two traits
        - The cross product of two 3:1 ratios is 9:3:3:1

Again a physical factor is involved

Mendel

- DID not consider the actual physical entity that controls experiments
    - Others discovered that entity

Other experiments determined

- Mendel's factors (genes) reside on chromosomes
- DNA was the heredity material.

Naming the Mendelian Laws

- **Correns (1900)**
    - Referred to segregation and assortment
- **Morgan (1916)**
    - First to use the terms:
        - ***Law of Segregation***
        - ***Law of Independent Assortment***

Concept 1 Confirmed: Genes control phenotypes

Genes Reside on Chromosomes

Eduard Strasburger (1876)

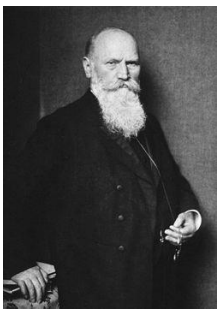
- Cell division is a universal activity of all higher organisms
    - Same process is observed in plants

Walther Flemming (1878)

- Structures had a string like appearance to them
    - Termed the structures chromatin (or colored substance)
- Also developed the concept of cell division
    - ***Called cell division mitosis***.

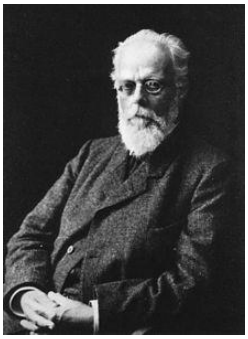
Edouard van Beneden (1883)

- Egg cell + sperm cell fertilization
  - Resulting cell has the diploid chromosome number
- Sperm and egg cell
  - Each contribute equal numbers of chromosomes to the zygote
- Discovered meiosis



Heinrich Wilhelm Gottfried von Waldeyer-Hartz (1888)

- Called the structures dividing during mitosis chromosomes
  - ***Chromosomes (=colored bodies)***



August Weismann (1892)

- Germline Theory
  - Sperm and egg cells
    - Contain exactly half the number of chromosomes
      - ***Transmit hereditary information***
  - Somatic cells
    - Carry out normal body functions

Hugo deVries (1889 on)

Performed hybridization experiments and discovered

- ***Each trait controlled by a different factor***
  - Observed 3:1 ratio in F_2
- Called the hereditary factor a ***pangene***
- Individual pangenes controlled all traits
  - Pangenes located in the cell of a diploid organism

Initially unaware that Mendel proved this earlier

- Later tried to publish without referencing Mendel
  - Correns corrected him
    - ***Admitted that Mendel was the first to discover the laws of genetics***

Considered pangenes

- Larger than a single chemical molecule
  - But still invisible

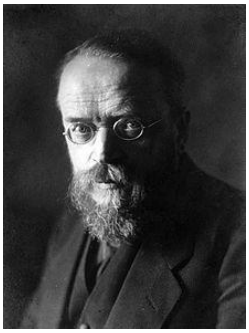
Reproductive cells

- Receive half of the pangenes during meiosis
  - When reproductive cells unite
    - Diploid number of pangenes is restored

See: van Beneden, Weismann above for comparison

First linkage between inheritance and reproductive cells

=Pangenes



Carl Correns (1900)

- Study inheritance in plants
  - Published results in paper
    - "G. Mendel's Law Concerning the Behavior of the Progeny of Racial Hybrids"

Mentions Mendel in title

Erich Tschermak (1900)

- Plant breeder working on wheat, barley, and oats
  - Tried to combine earliness and high yield
    - Considered the "father" of Austrian plant breeding
- Did genetic experiments with pea
  - ***Referenced Mendel in his publication***

Rediscovering Mendel's Concepts of Genetics

- **Referenced in publications by:**
  - DeVries (April 1900)
  - Correns (May 1900)
  - Tschemark (August ??? 1900)

Chromosome Theory of Inheritance (1902-1903)

Chromosomes are the carrier of Mendelian factors and meiosis is the basis of separating the factors into gametes.

Also predicted a mutation in a single cell leads to uncontrolled cancer cell growth

Theodor Boveri (1902)

- Observed
  - All male and female chromosome must be present to develop a functioning organism
  - Linked chromosomes and the factors that were described by Mendel
- Quote
  - ***"… the characters dealt with in Mendelian experiments are truly connected to specific chromosomes."***

Note the similarities in the quotes

Walter Sutton (1902)

- Described chromosomes as unique individual units
  - That occur in pairs
  - Separate during meiosis
- Quote
- ***Chromosomes "…may constitute the physical basis of the Mendelian law of heredity."***

Linking Genes and Chromosome

Thomas Hunt Morgan and Calvin Bridges

Headed "The Fly Lab" at Columbia University
*****Many of his students made other genetic contributions**

Thomas Hunt Morgan (1910)

- Discovered a mutant white eye Drosophila
  - Different than the wild type red eye
- Performed genetic experiments
  - ***Results proved the eye color gene was located on the X chromosome***

Calvin Bridges (1914)

- Studied Morgan's white eye mutant
  - Coupled the presence of the X chromosome with a specific eye color
  - ***Conclusively demonstrated genes indeed reside on chromosomes***

Problem with this concept!!

- Chromosomes carried the genetic information
  - They must contain all the genetic factors
- But, the number of chromosomes is less than the number of traits.
  - ***Now it was essential to show chromosomes contain many factors***

Solution: Multiple Genes Reside on Chromosome!!

- **Sturtevant, Bridges, Morgan (1919)**
  - Mated among *Drosophila* with several different contrasting phenotypes
    - Multiple genes are organized into a linear linkage group
      - ***Number of linkage groups equals the number of chromosomes***

It could now be stated:

All features necessary for a hereditary unit are found in chromosomes!!!

Finally, heredity and chromosomes are clearly linked.

Concept 2 Confirmed: Genes reside on chromosomes

Position Effect

Sturtevant (1925)

- If the physical environment of a gene is altered
  - Expression of the gene is affected
- Therefore
  - ***Physical structure of the chromosome is essential for the correct phenotypic expression***

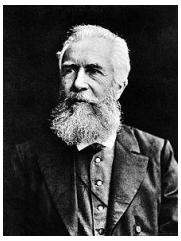
Concept not fully appreciated by most genomic researchers

From a modern perspective

- This is the first solid evidence that we should take a ***genomics approach*** to fully understand gene expression.
- Therefore
  - ***Completely characterizing (=sequencing) all of the genetic material in the cell is necessary.***

SO WHAT IS THE GENETIC MATERIAL???

History of DNA As the Genetic Material



Ernst Haeckel (1866)

- Nucleus transmitted hereditary information to the next generation

Friedrich Miescher (1871-1874)

Studied pus cells collected from bandages from surgeries

- Collected white blood cells
- White blood cells primarily composed of nuclei
  - ***Called this nuclear material nuclein***

Determined that nuclein contained two classes of chemicals

- **Acidic component**
  - *Now we know the component is* ***DNA and RNA***
- **Basic component**
  - *Now know that is* ***histone proteins***

Which chemical is the stuff of life??
****nucleic acids??**
****proteins??**
Most abundant molecules
****Nitrogen**
****Phosphorus**

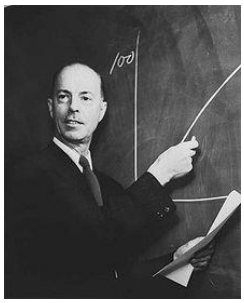
Linking DNA and Heredity

Fred Griffith (1928)

- Worked with lethal and non-lethal strains of the *Streptococcus pneumoniae*
    - Converted a non-lethal strain to a lethal strain
- Conversion involved
    - Mixing dead lethal and live non-lethal strains

Griffith's Transforming principle

- Converts one phenotype to another
    - This is the true nature of a gene
    - ***These are two alleles of the same gene***
- ***So what is the chemical nature of the transforming principle????***


Oswald Avery **Colin MacLeoud** **Maclyn McCarty**

Avery, MacLeod, and McCarty (1944)

- **Transforming principle**
  - **DNA was the transforming principle(from the acidic component)**
  - Not protein or RNA
    - The other two constituents in the nucleus.

Concept 3 Confirmed: Chromosomes consist of DNA

RNA Is Also A Genetic Material

- **Heinz Fraenkel-Conrat (1957)**
  - RNA viruses exist
    - Interconverted strains of tobacco mosaic virus
      - ***RNA mediated the interconversion and can be a genetic material***

Chemical Structure of DNA


James Watson and Francis Crick (1953)

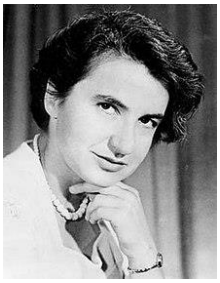
- DNA is double-stranded
- Strands are oriented in an anti-parallel manner to each other
- Purines nucleotides are opposite pyrimidines nucleotides
    - Guanine hydrogen bonds with cytosine
    - Adenine hydrogen bonds with thymine
- Structure is stabilized by
    - Hydrogen bonds
    - Hydrophobic bonding between stacked bases

Watson and Crick

- Did not perform any experiments
    - Based on research of others

Research results of others that aided Watson and Crick

- **Erwin Chargaff**
  - Concentrations of guanine and cytosine were always equal in DNA
  - Concentrations of adenine and thymine were equal in DNA



- **Rosalind Franklin** and **Maurice Wilkins**:
  - Used X-ray crystallography to study structure of DNA

Clearly showed DNA was a two-stranded molecule

Watson and Crick major contributions to describing the structure of

- DNA had a repeating structures (nucleotides)
- DNA was of a constant width
- DNA was double-stranded