SYNGAP1 Family Meet-Up – 11/9/2019

Genetics 101

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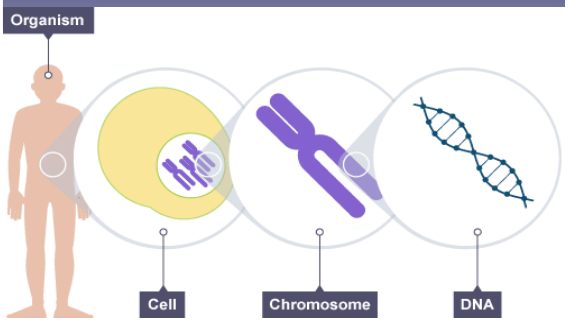
Conflicts of Interest

* None.

Overview

* Fundamental elements of Genetics
* *SYNGAP1* gene
* Genetic Changes (Variants)
* Inheritance
* Questions

Fundamentals of Genetics



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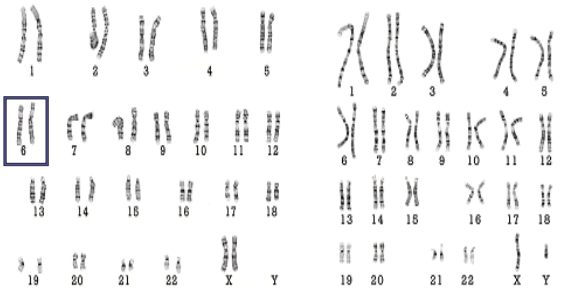
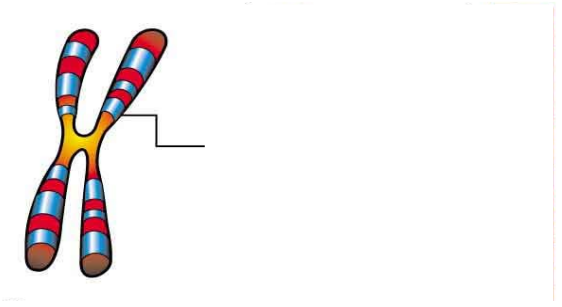
Chromosomes



http://health.hawaii.gov/genetics/files/2013/05/xy.gif

Chromosomes → Genes → DNA



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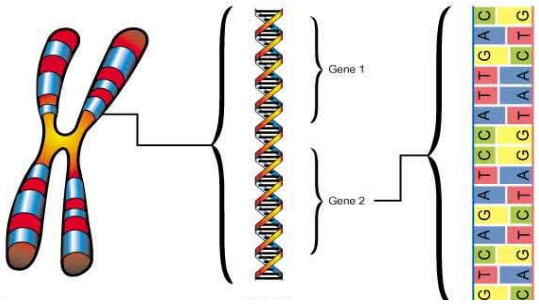
Chromosomes → Genes → DNA



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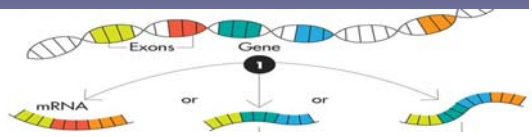
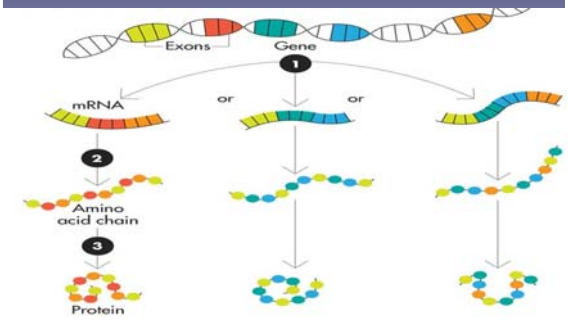
Genes → Protein



https://cdn.zmescience.com/wp-content/uploads/2016/01/DNA_exons_introns.gif

Genes → Protein

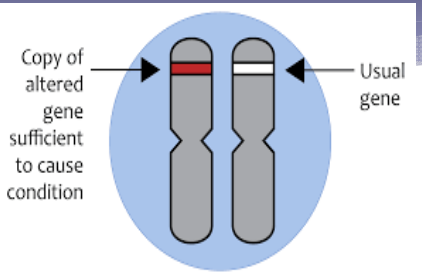


https://cdn.zmescience.com/wp-content/uploads/2016/01/DNA_exons_introns.gif

SYNGAP1

- Location: chromosome 6p21.32
- The *SYNGAP1* gene provides instructions for a protein (SynGAP) that plays an important role in nerve cells in the brain.
- Genetic changes in *SYNGAP1* have been associated with intellectual disability, epilepsy, and autism spectrum disorder
  - Autosomal dominant condition: having a genetic change in one copy of the gene is sufficient to cause the condition
    - Heterozygous: genetic change is present in one copy of the gene
- Mechanism: the genetic change causes a loss of protein function resulting in haploinsuffiency
  - Having one functioning copy of the gene is not enough

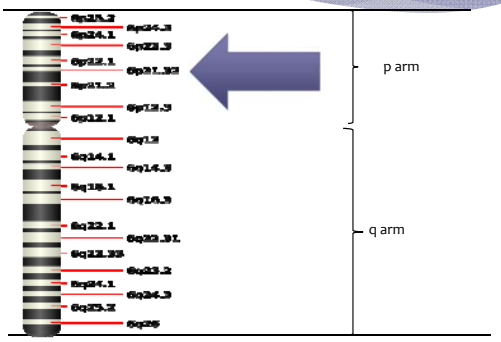
Autosomal Dominant



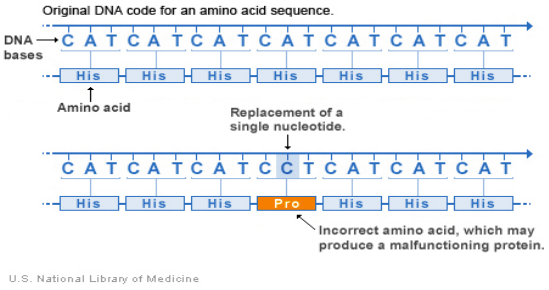
Genetic Changes = Variants

- Everyone has genetic changes
  - Unique, normal changes
  - **Disease causing (pathogenic)**
- Different types of variants causing loss of protein function:
  - Whole/partial gene deletion
  - Missense
  - Nonsense
  - Frameshift due to insertion/deletion
- Variants are reported based on position and type of change:
  - DNA: c.1685 C>T
  - Amino acid: p.Pro562Leu

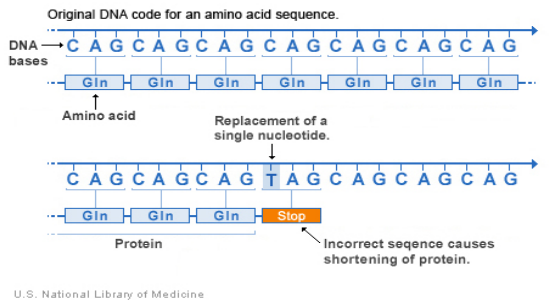
6p21.32 Deletion



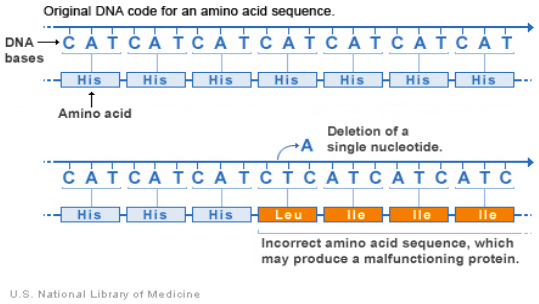
Missense



Nonsense

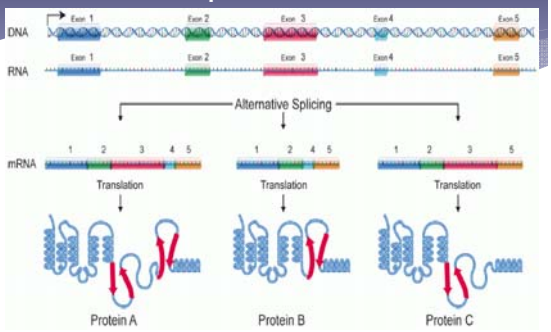


Frameshift



U.S. National Library of Medicine

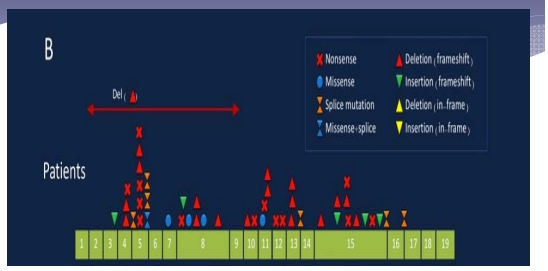
Splice Site



Genetic Testing

- The purpose of genetic testing is to identify variant(s) that explain an individual's medical history.
  - Examples of genetic tests:
    - Whole exome sequencing
    - Panel
    - Chromosome microarray

SYNGAP1 Variants



http://epilepsygenetics.net/syngap1-this-is-what-you-need-to-know/. Adapted from Mignot et al., 2016)

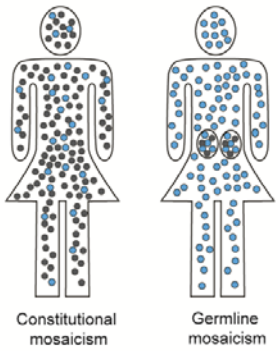
Variable Expressivity

- Variable expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition.
  - Can be attributed to multiple factors (i.e. other genetic variants)
    - Example: individuals with larger 6p21.3 deletions may have other genes included that also play a role in brain development

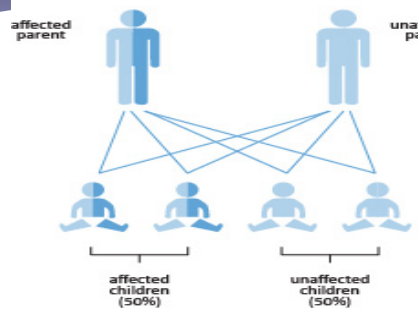
Inheritance

- Majority of cases are de novo (brand new in person tested).
  - Variant is not detected in samples provided from mother and father
- Possibility of mosaicism:
  - Germline mosaicism: variant is present in either sperm or egg cells of the parent
    - This is one explanation if there are multiple affected children
  - Somatic mosaicism: variant is present in some, but not all cells
    - As reported in a mildly affected father of an affected child

Mosaicism



Autosomal Dominant Inheritance



Questions?