PMSF Symposium
Genetics 101

Jon Bernstein MD, PhD
Associate Professor of Pediatrics
Stanford School of Medicine
7/29/2017

Outline

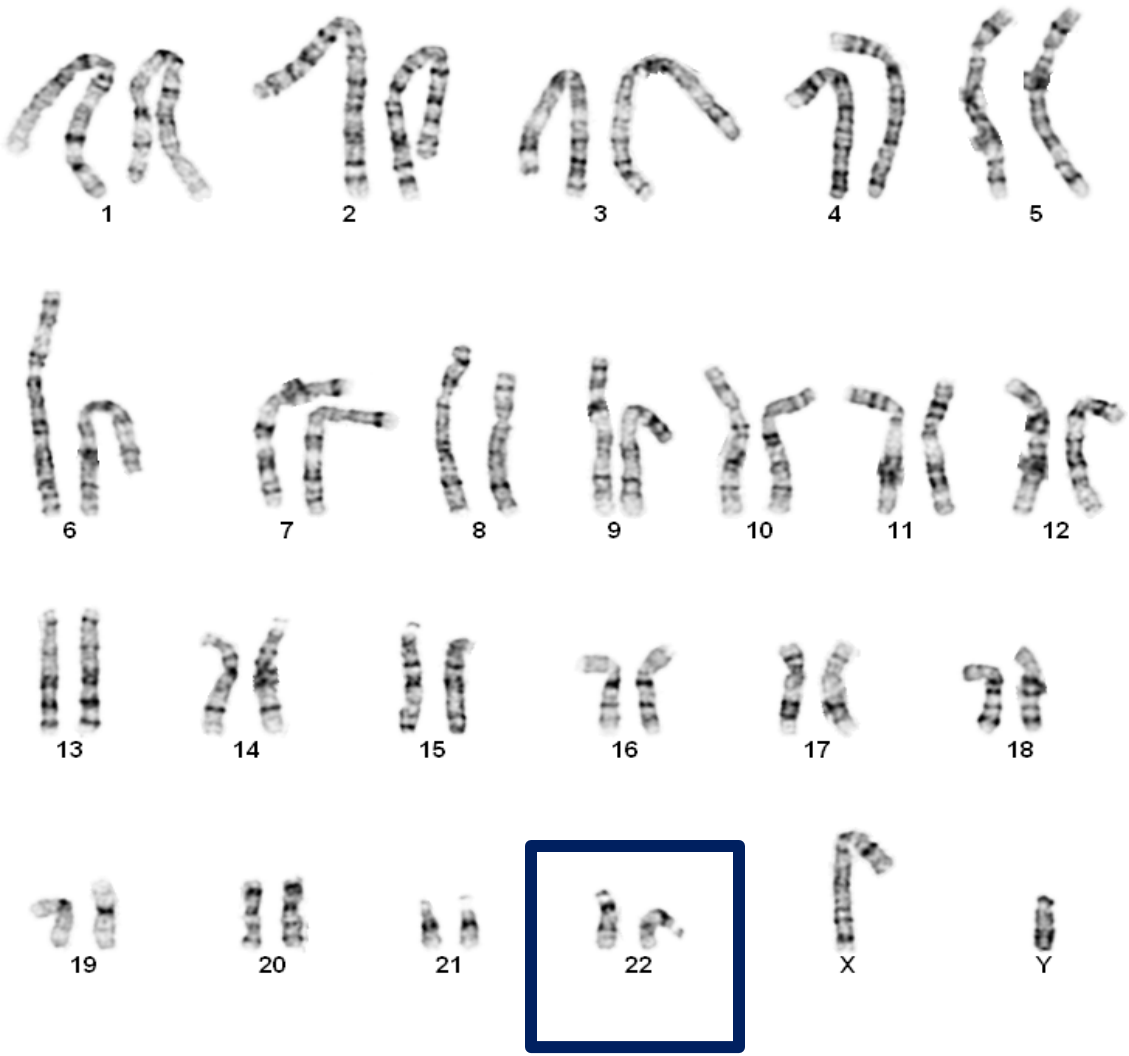
- Overview of genetic terminology
- Types of genetic mutation related to Phelan-McDermid syndrome and how they are detected
- Relationships between mutation type and characteristics and manifestations of the condition

*Note that the material presented is not necessarily applicable to all families with Phelan-McDermid syndrome or other genetic conditions. Professional consultation should be obtained to guide interpretation of genetic testing results.

Phelan-McDermid Syndrome

- Intellectual disability, autism
  - Limited to absent speech
  - Greater receptive than expressive communication
- Seizures
- Increased pain tolerance
- Limited mobility
  - Delayed ability to walk, unsteady gait, unable to walk
- Characteristic physical features
  - Thin toenails, large fleshy hands

The Human Genome

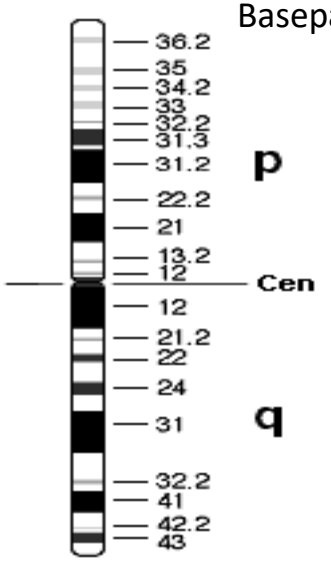


Athena Cherry, PhD Stanford Cytogenetics

Describing Chromosomes

#1

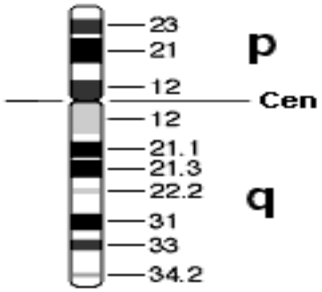
Basepair #1



Basepair #247 Million

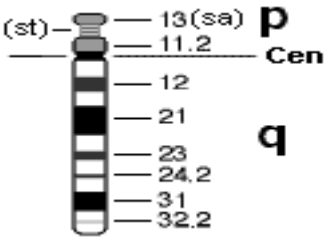
Metacentric

#9



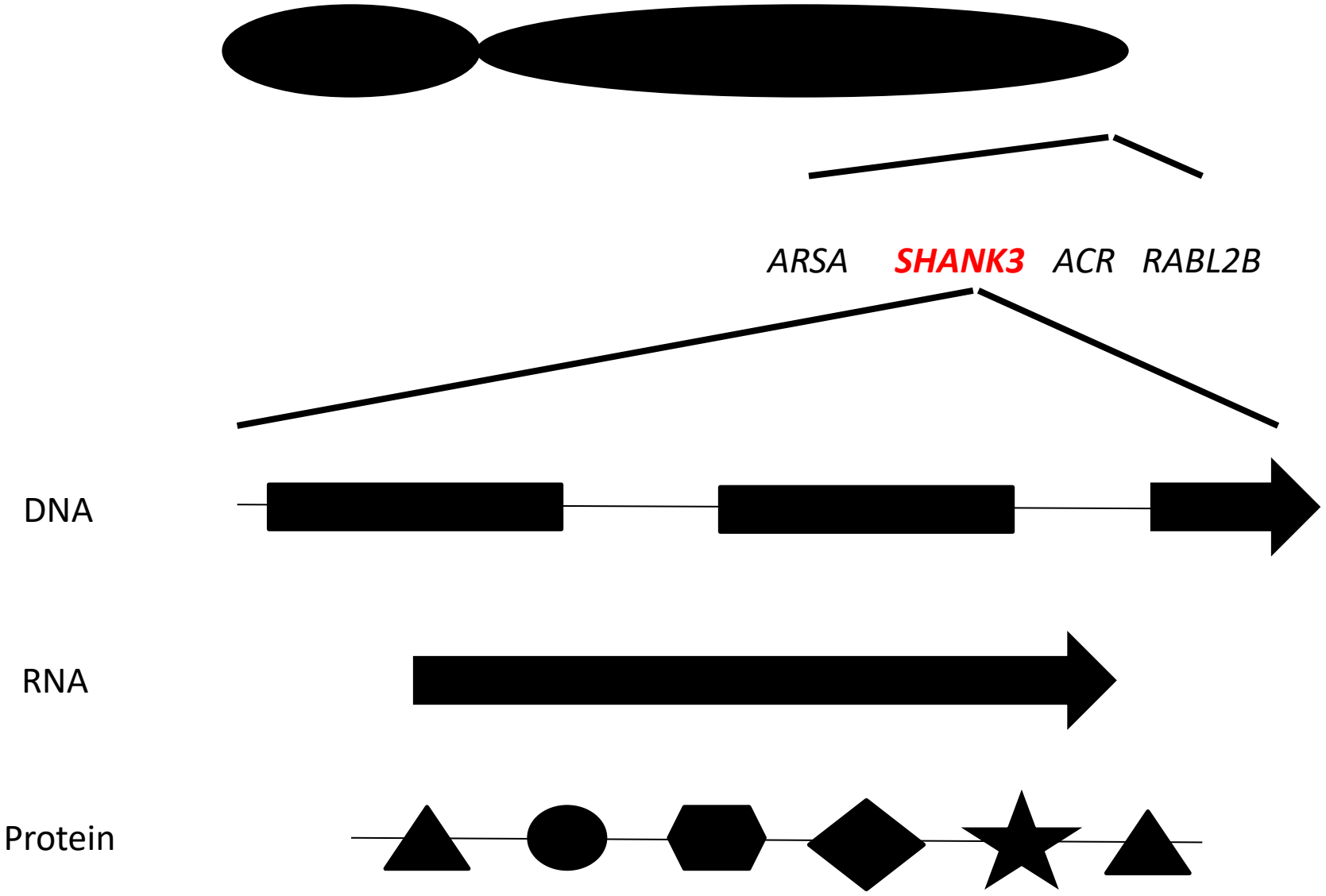
Submetacentric

#14

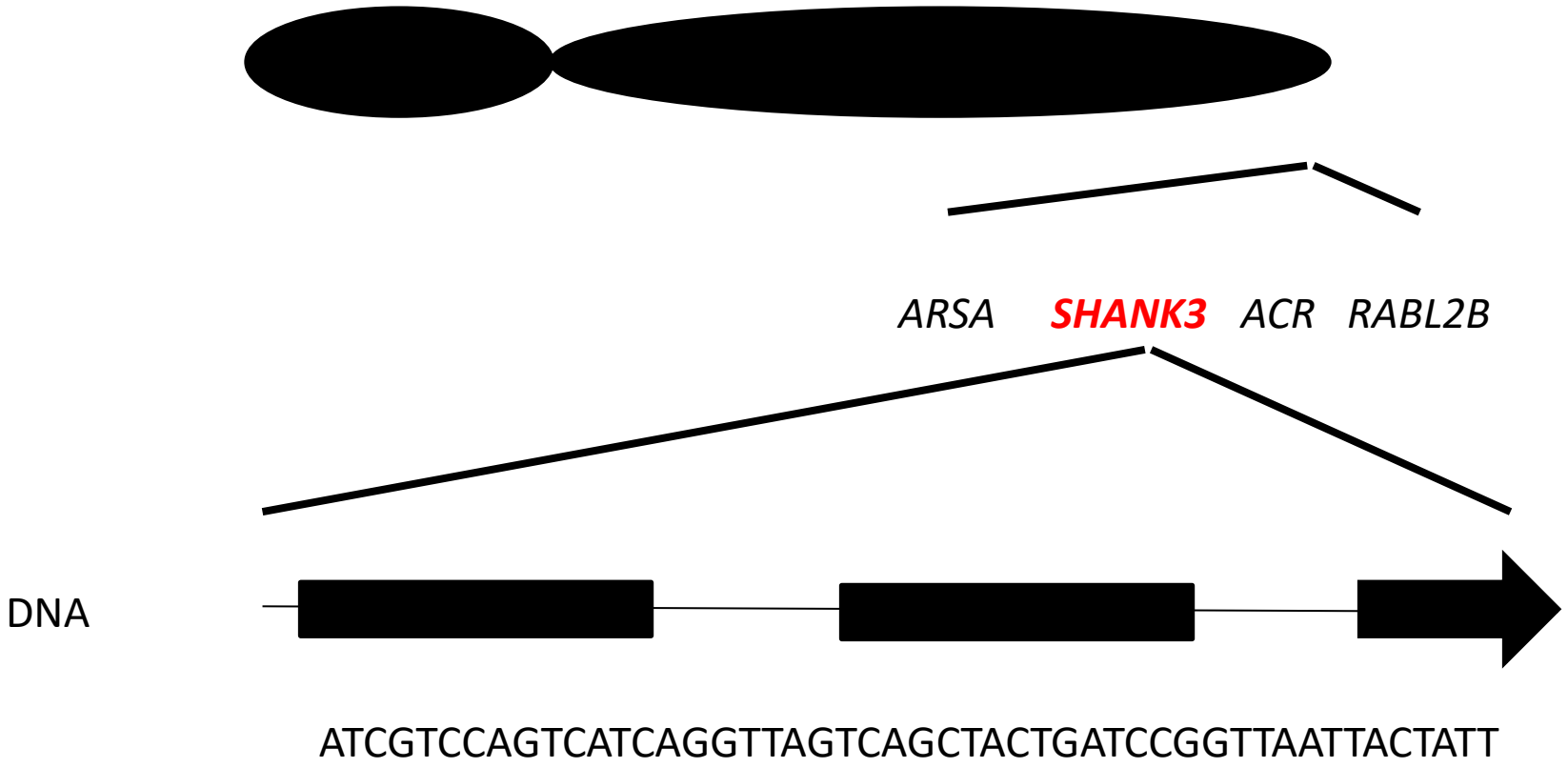


Acrocentric

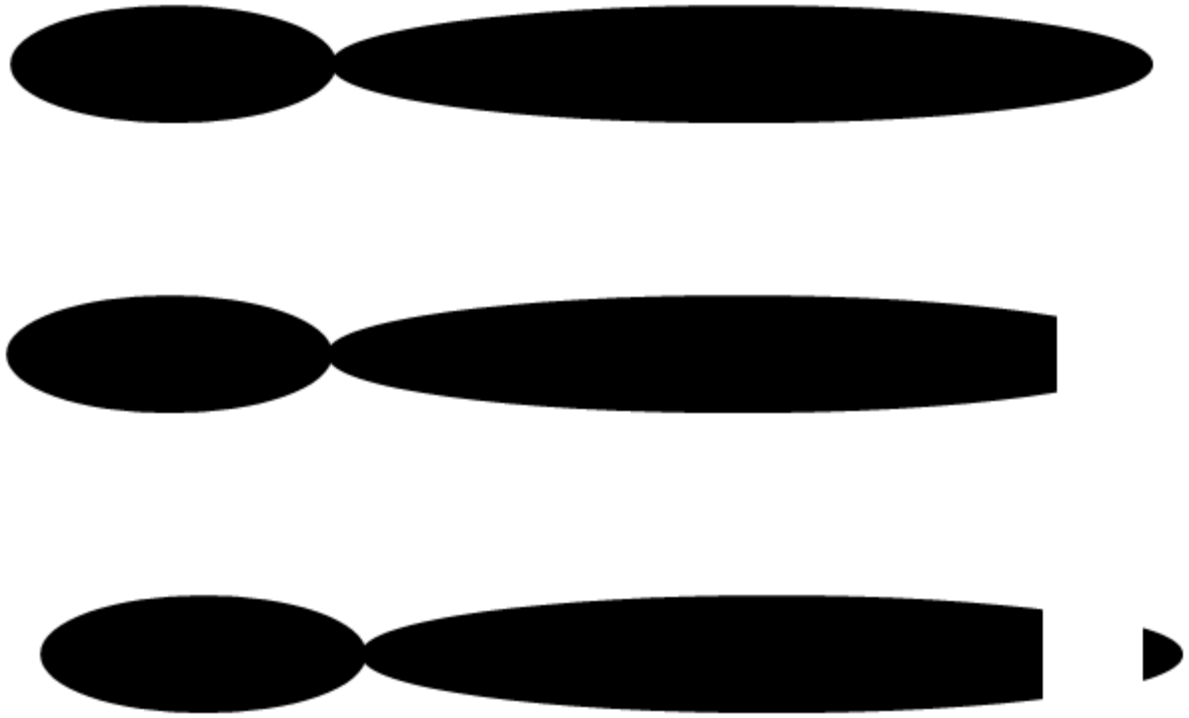
Distal Chromosome 22



Scales of Genetic Variation



Deletions



Interstitial Deletions

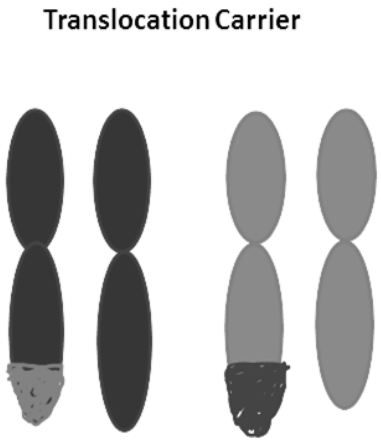
Interstitial

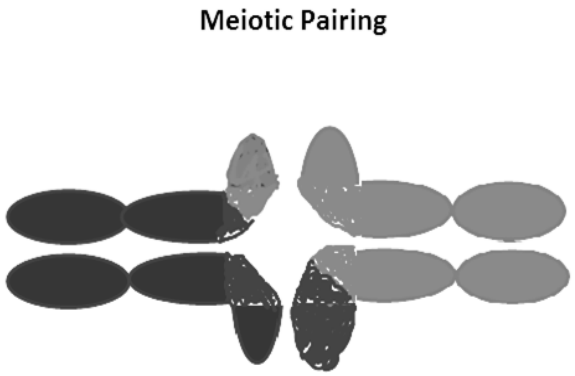
- Many interstitial deletions are new or *de novo*
- Individuals with an interstitial deletion in *SHANK3* typically have a 50% of passing it on.
- If parents do not detectably have the deletion or a predisposing genetic change in their blood the likelihood of another family member having the same mutation are reduced, but not eliminated.

Terminal Deletions

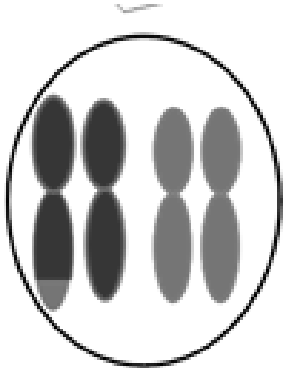
Terminal

Balanced translocation





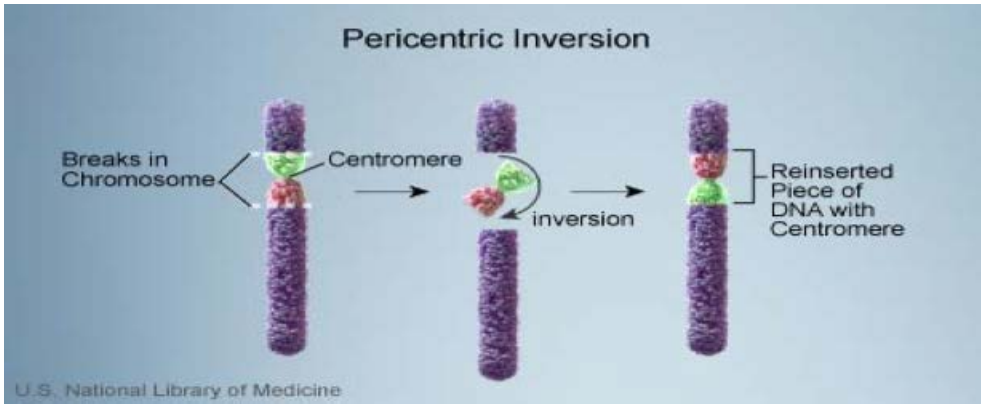
A balanced translocation in a parent
Can lead to an unbalanced translocation
In a child and is therefore associated with
an increased risk of familial recurrence



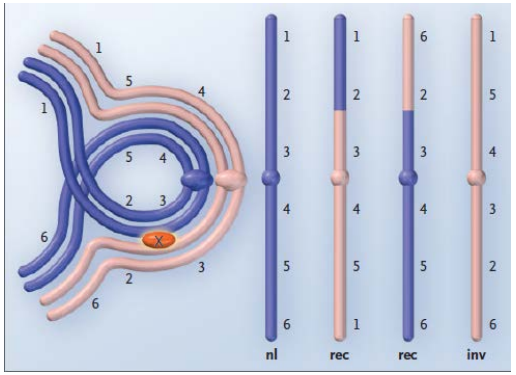
Terminal Deletions

Terminal

Balanced inversion



A balanced inversion in a parent
Can lead to an unbalanced inversion product
In a child and is therefore associated with
an increased risk of familial recurrence



Stoler et al., N Engl J Med 2004;351:2319-26.

Terminal Deletions

Terminal

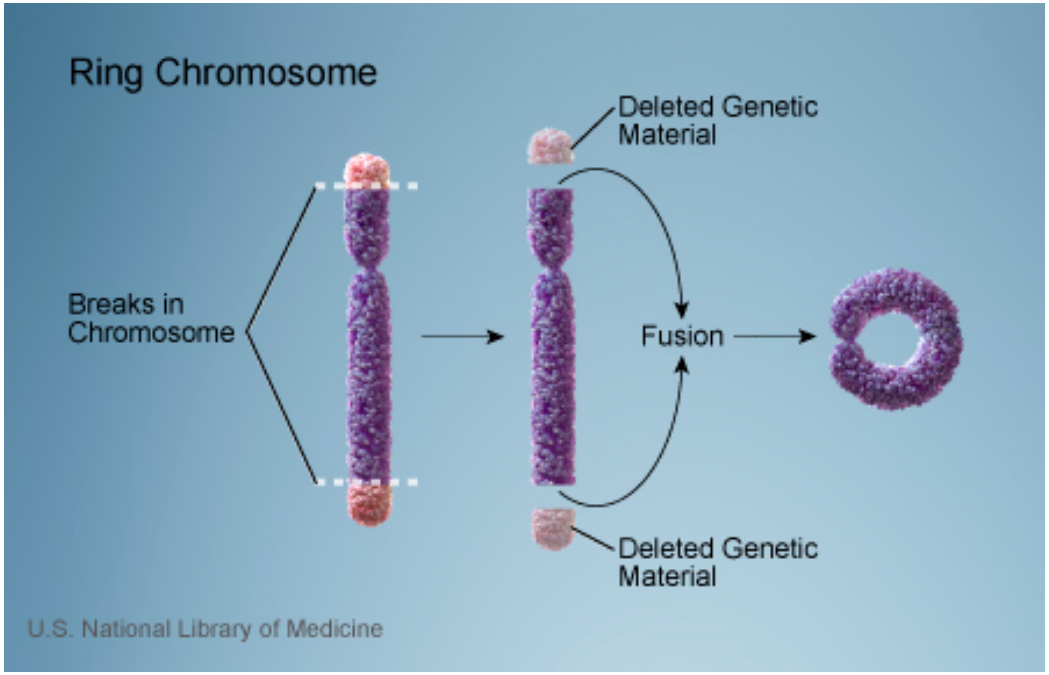
- Some terminal deletions are new or *de novo*
- Individuals with an interstitial deletion in *SHANK3* typically have a 50% of passing it on.
- If parents do not detectably have the deletion or a predisposing genetic change in their blood the likelihood of another family member having the same mutation are reduced, but not eliminated.
- Unbalanced translocations can also be new or *de novo*, however, they can also arise from a translocation in a parent

Translocations and Inversions

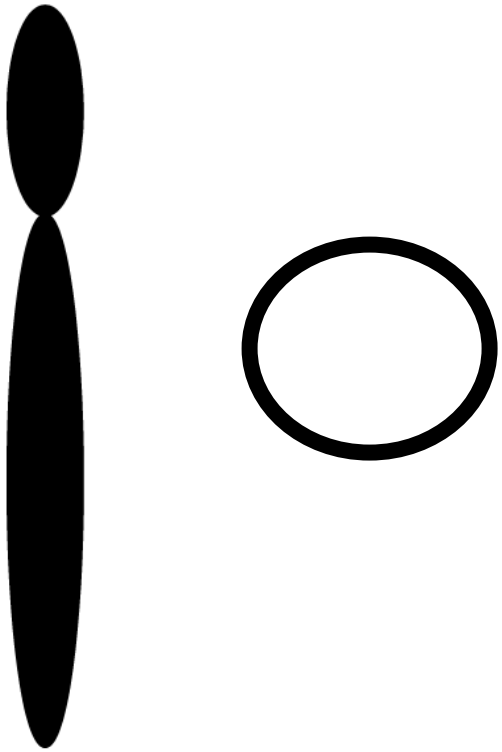
- Terminal deletions resulting from translocations or inversions typically have an accompanying duplication.
- Investigation for a these rearrangements is recommended even when the duplication is not initially detected.

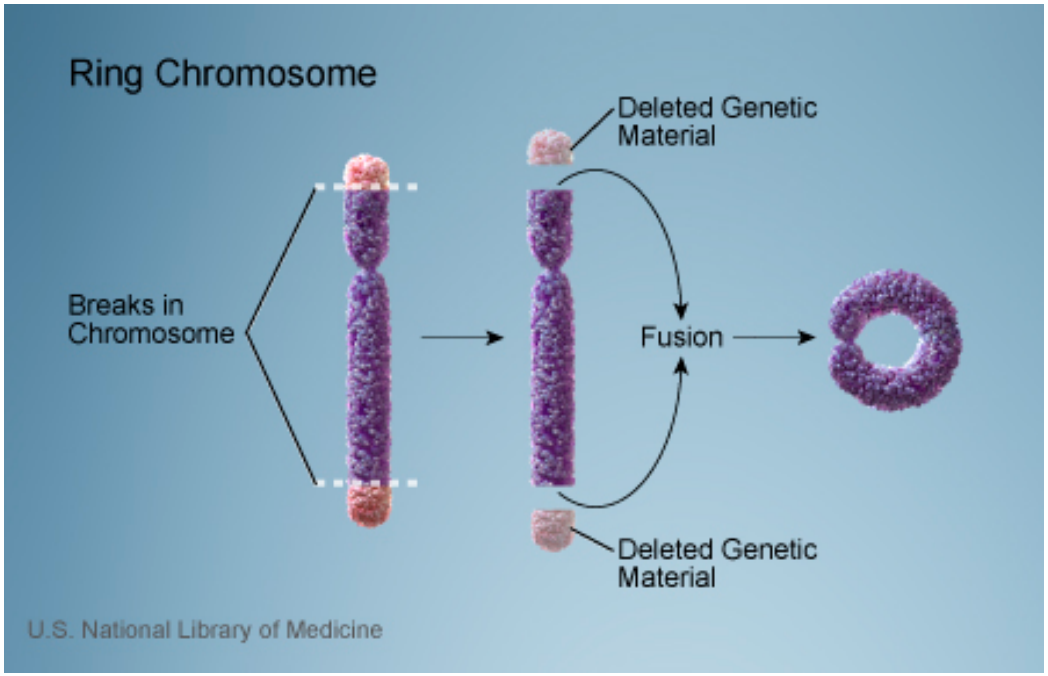
Terminal Deletions

Terminal



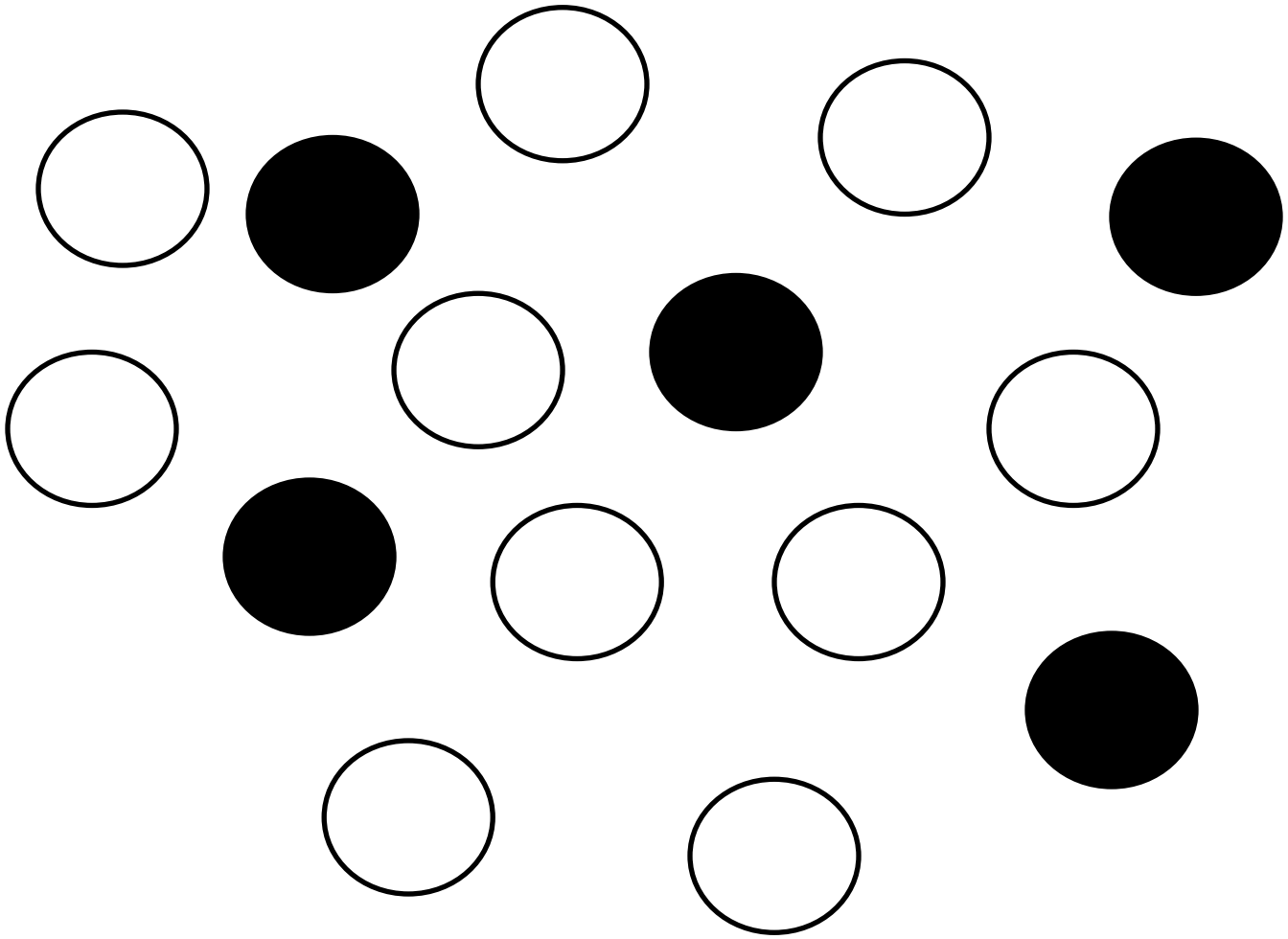
Ring chromosomes





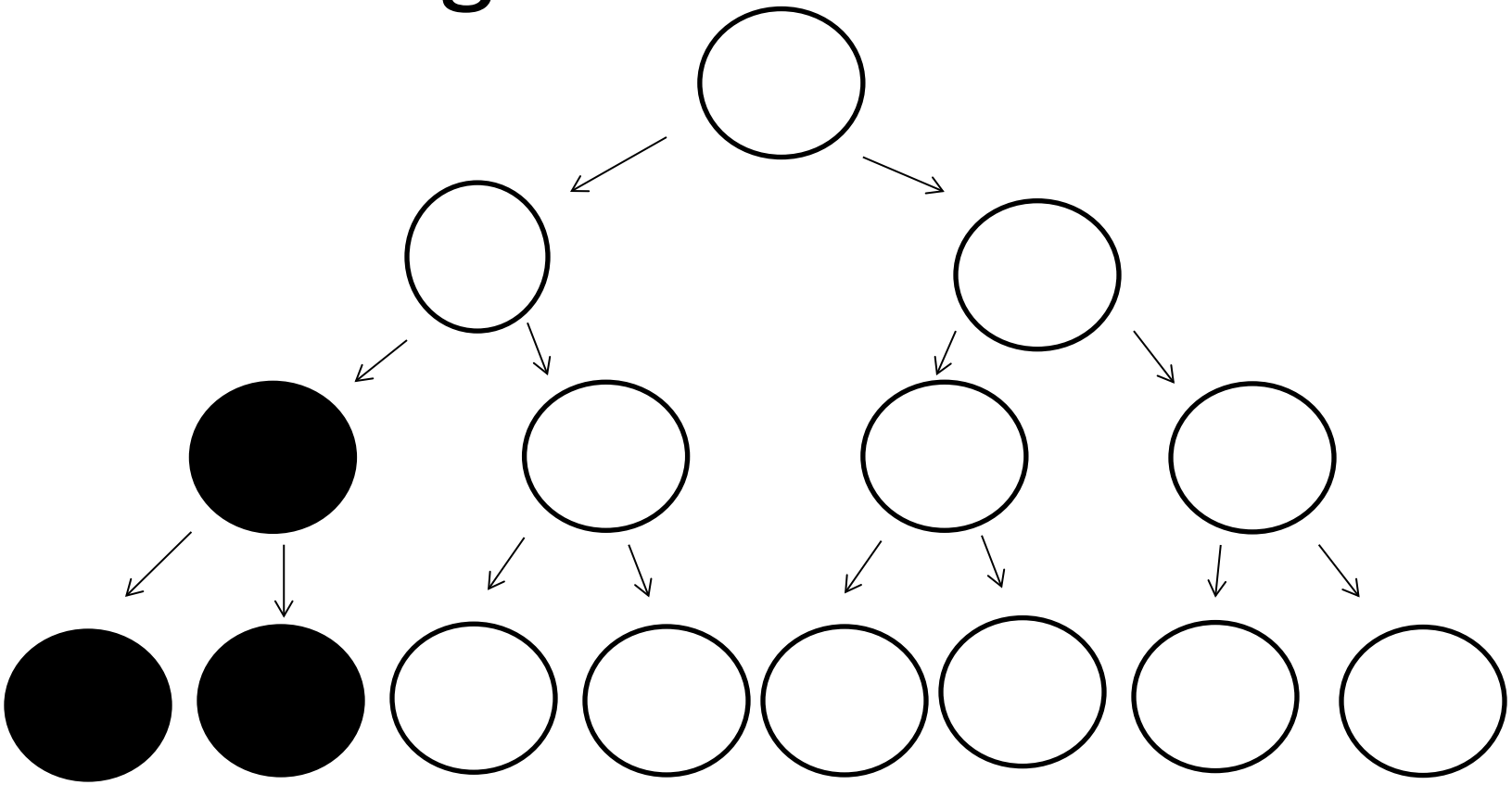
- Ring chromosomes are often mosaic and can be unstable
- If chromosome 22 is lost cell there can be a risk of medical complications including tumors

Mosaicism

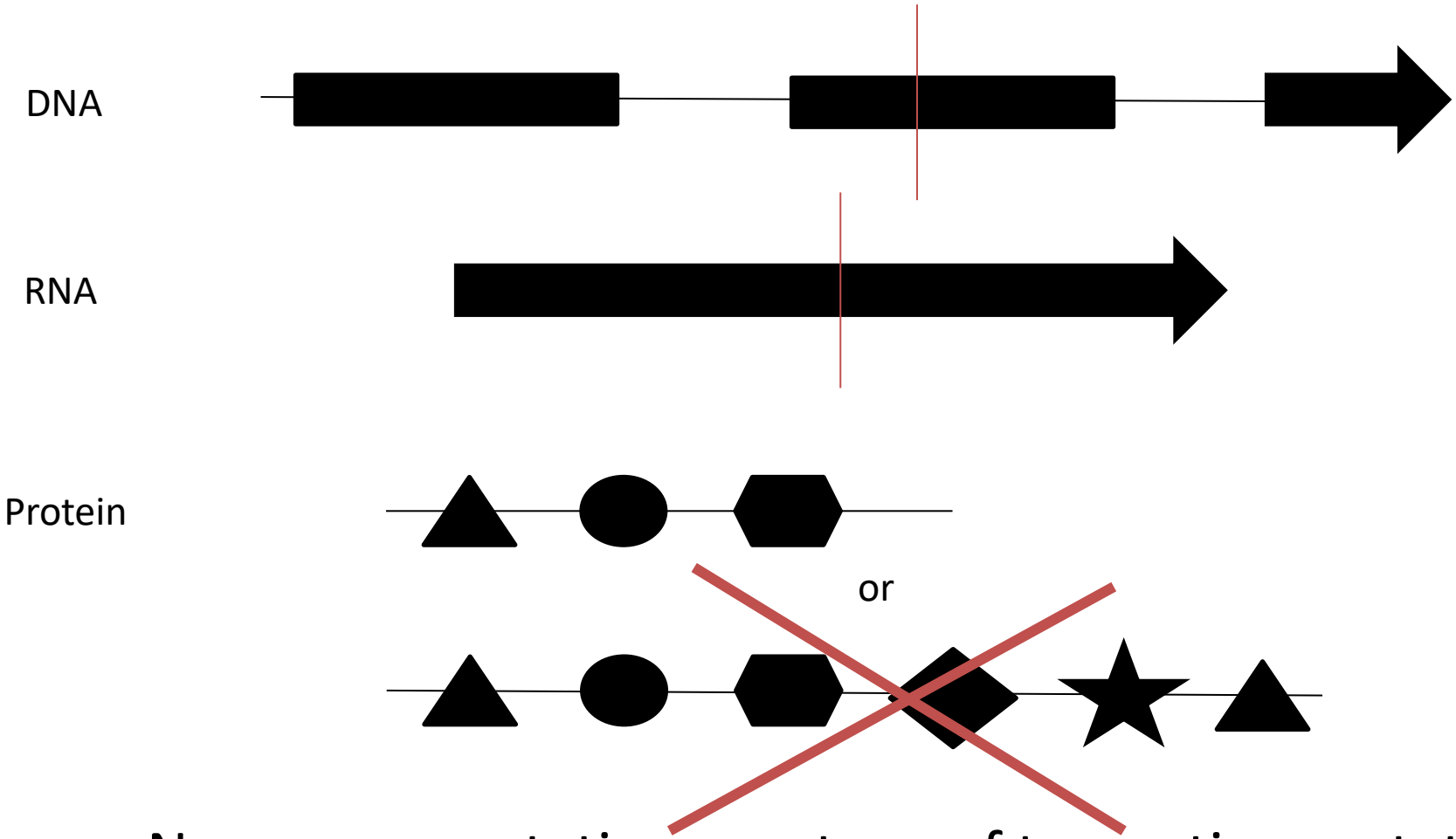


Some cells have a specific genetic change while others do not

Origin of Mosaicism

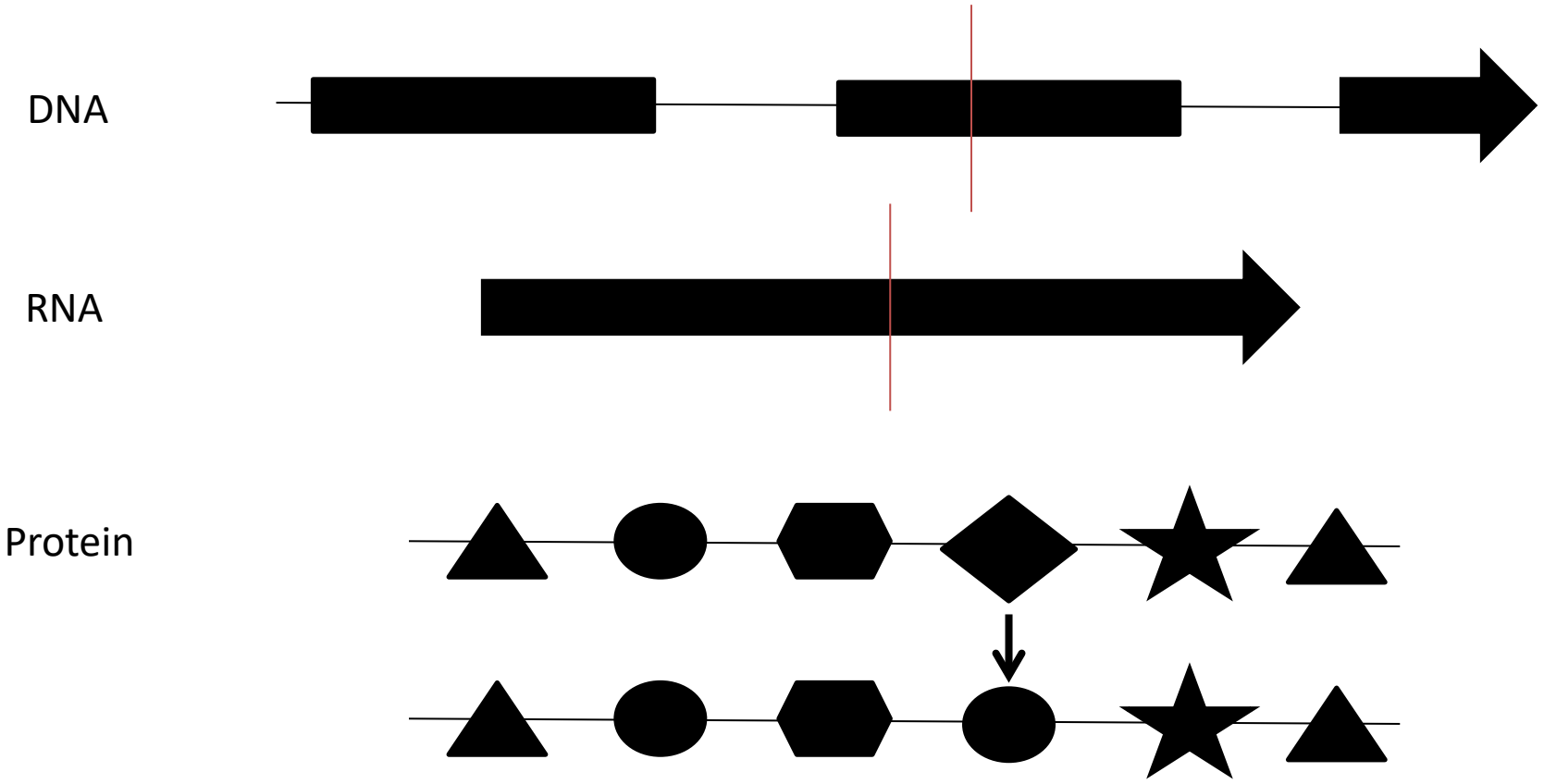


Point mutations



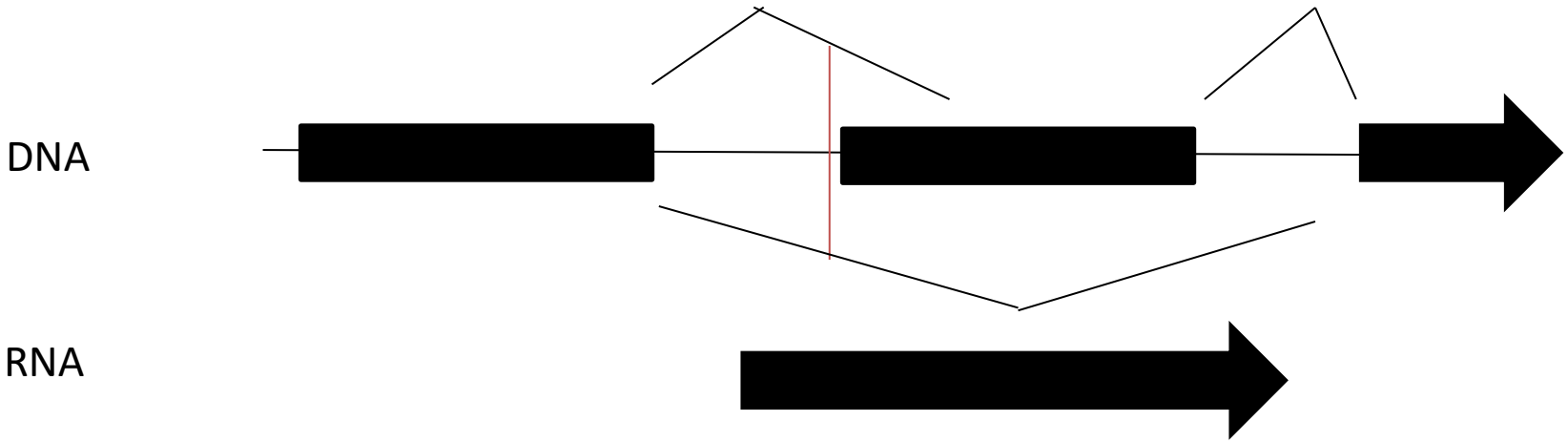
Nonsense mutations – a type of truncating mutation

Another type of point mutation



Missense mutation

Another type of point mutation



Splice mutation – one example

Point mutations

- Many point mutations are new or *de novo*
- Individuals with a point mutation in *SHANK3* typically have a 50% of passing it on.
- If parents do not detectably have the point mutation in their blood the likelihood of another family member having the same mutation are reduced, but not eliminated

Variants vs mutations

- Are all genetic changes strongly associated with a medical condition – No
- Variant – a genetic change that differs from the most commonly seen version of a particular location in the genome
- Mutation – a variant that is associated with a medical condition or other genetic trait

Variants of uncertain significance

- For some variants it can be difficult to tell if it is a disease causing (pathogenic) mutation or a benign variant.
- Geneticists use a rating scale to roughly estimate the chance that a variant of uncertain significance is disease causing

Relationships between genotype and phenotype

- How “severe” is a particular mutation?
- In general it is difficult to predict
  - Some trends have been suggested
  - The smallest deletions and point mutations appear to be associated with an incomplete tendency towards less extensive language impairment

Sarasua et al., Human Genetics, July 2014, Volume 133, Issue 7, pp 847–859

- Why would the same mutation not always have the same outcome?

Summary

- Phelan-McDermid syndrome is a well known cause of developmental disability
- It results primarily, from disruption of the normal function of the *SHANK3*, potentially by one of a number of types of genetic mutation
- Different types of genetic variation are currently best detected by different types of genetic testing

Summary

- Understanding the specific type of genetic mutation can sometimes help guide medical care and help estimate the chance that multiple members of a family may have the condition