The Genetics of Phelan-McDermid Syndrome

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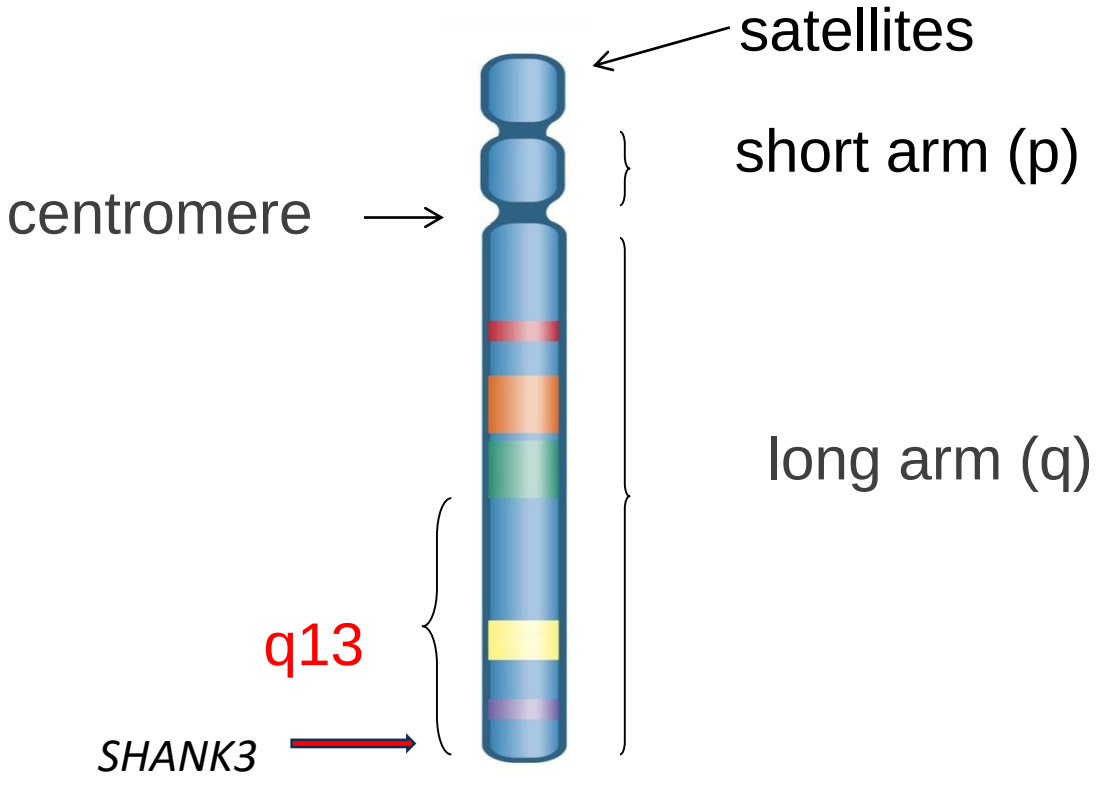
Causes of PMS

- **Deletion of 22q13 (86%)**
  - Terminal deletion – 1 break in the chromosome resulting in loss of the end of the chromosome
  - Interstitial deletions – 2 breaks in the chromosome resulting in loss of a segment within the chromosome but preservation of the end
- Pathogenic variant of the SHANK3 gene at 22q13.3 (14%)

PMS - deletion of chromosome 22q13



Chromosome 22

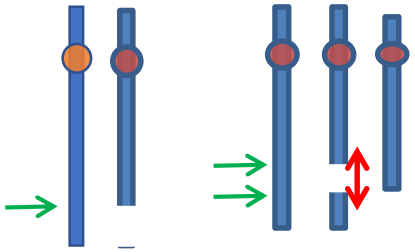
Testing Methods

- Chromosomal microarray (CMA)
  - Detects large deletions (copy number variants or CNVs)
  - Detection of terminal deletion of 22 should be followed by chromosome studies to r/o ring 22
- Gene Sequencing
  - Single gene testing – targeted testing of *SHANK3*
  - Multigene panel – for example, an autism panel
  - Genome or Exome sequencing – screens a vast array of genes
- Chromosome analysis (karyotyping)
- FISH – confirmatory test

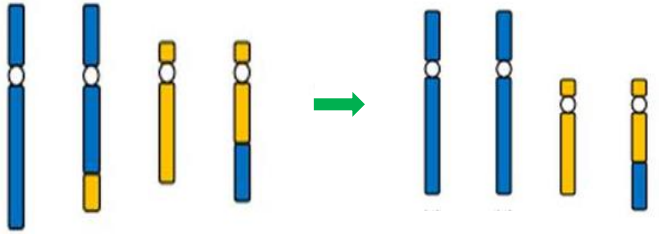
Chromosome Defects Leading to PMS

Deletions

Terminal *Interstitial*

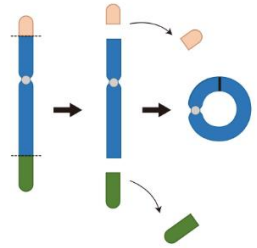


Translocations



t(16;22) der22

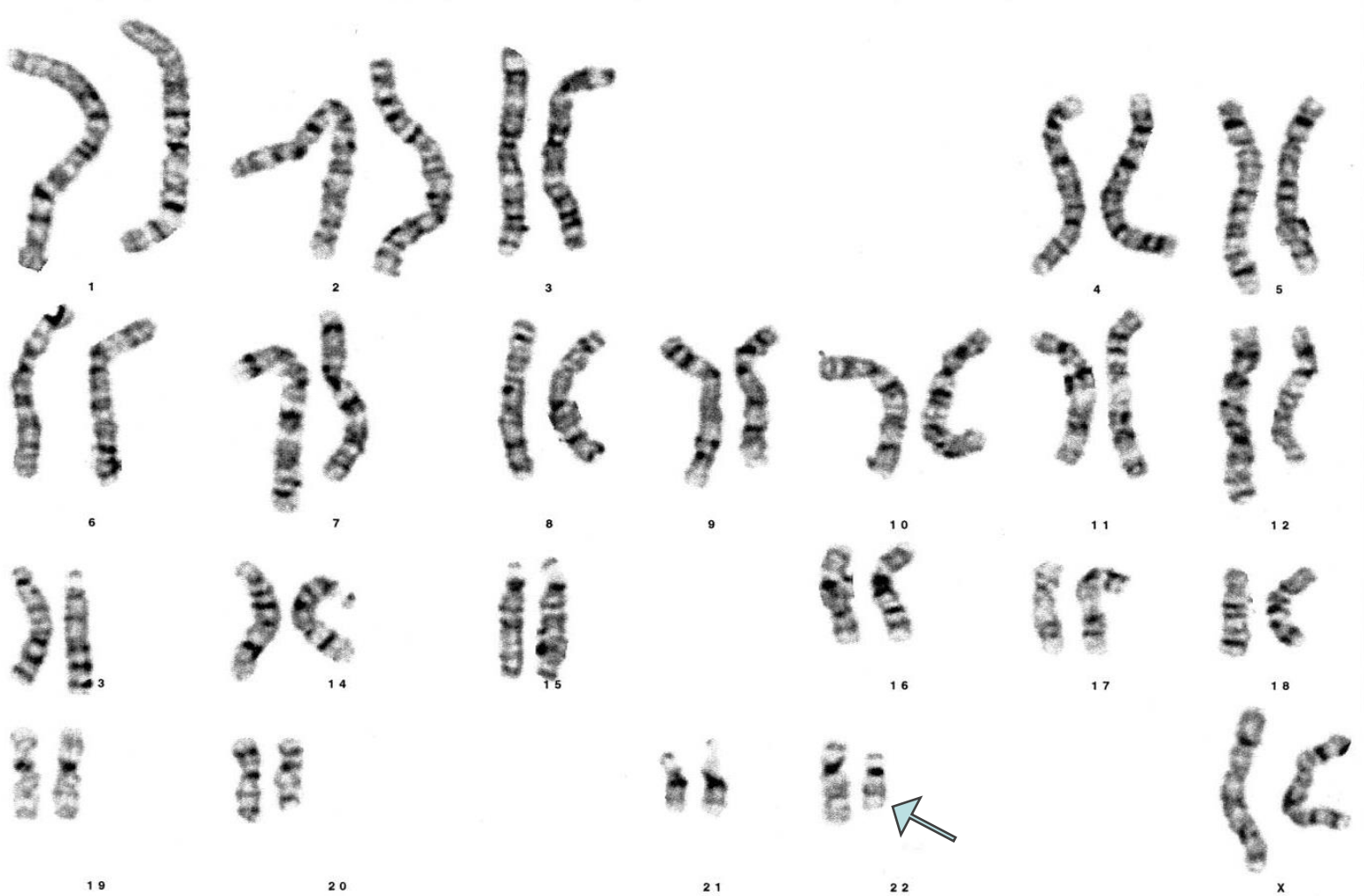
Ring chromosome



Ring 22

- *Deletion size ranges from <50kb to >9MB*
- *>70% of deletions occur on the chromosome 22 inherited from the father*

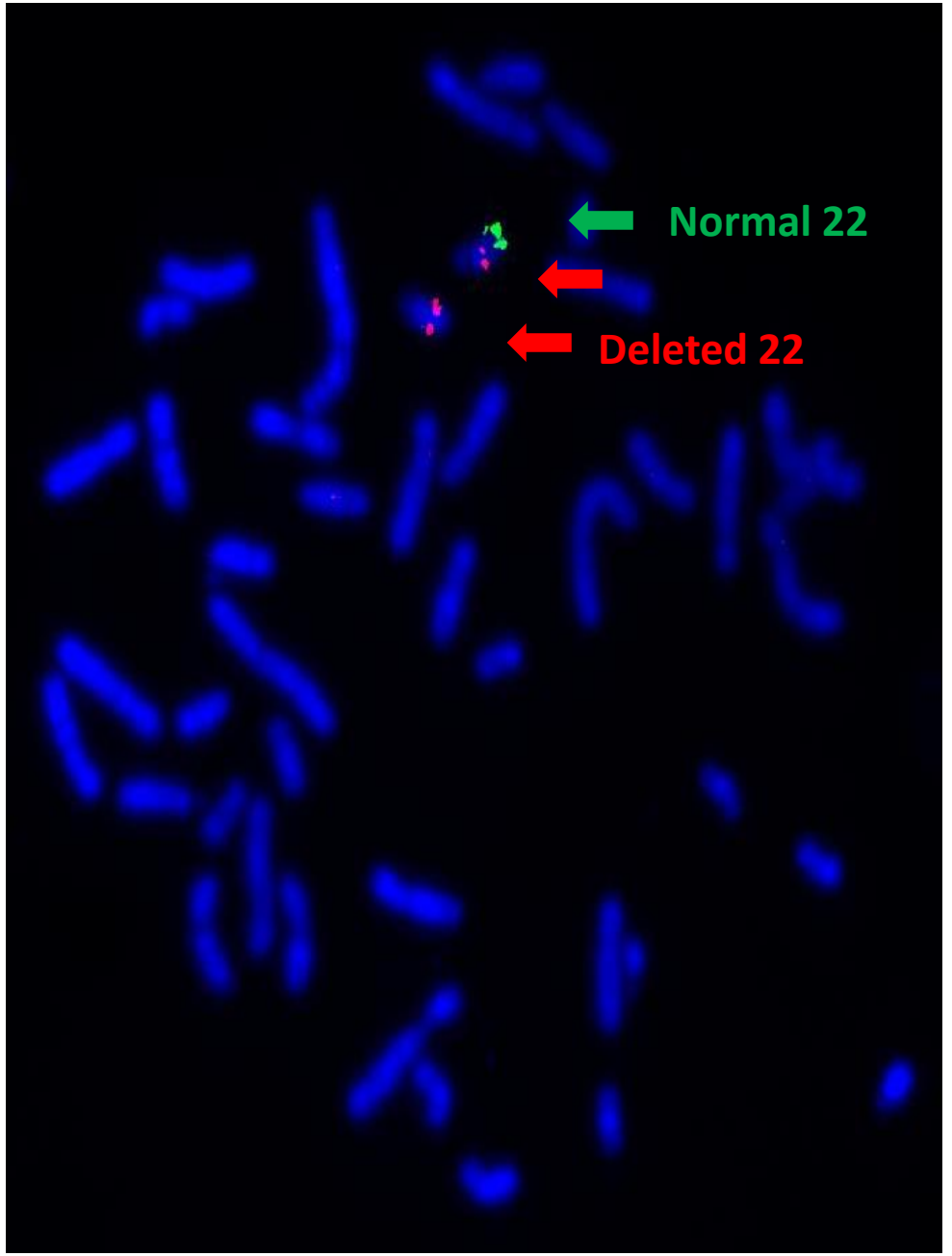
Deletion 22q13



FISH – deletion 22q13

Red = control probe

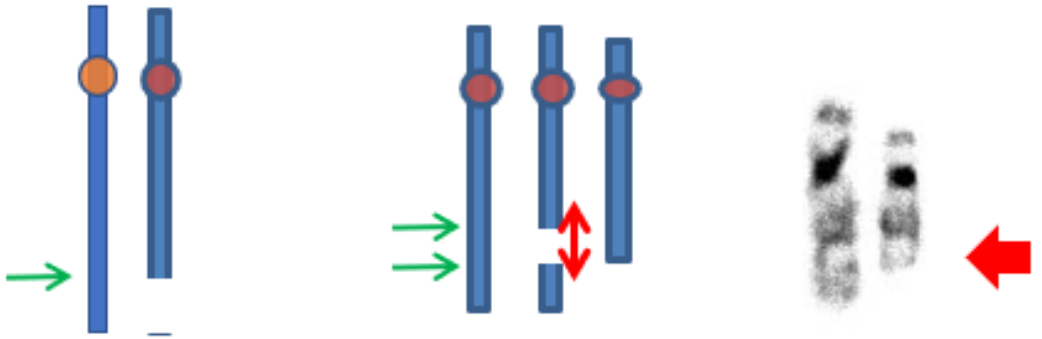
Green = probe for 22q13



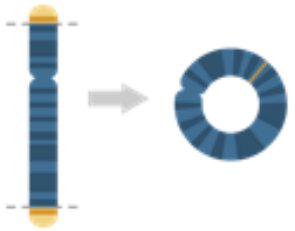
22q13 deletion:

- If a terminal deletion is detected by CMA, follow-up with chromosome studies to determine if it is a simple deletion or a ring 22

- ***Deletions*** *- terminal or interstitial*

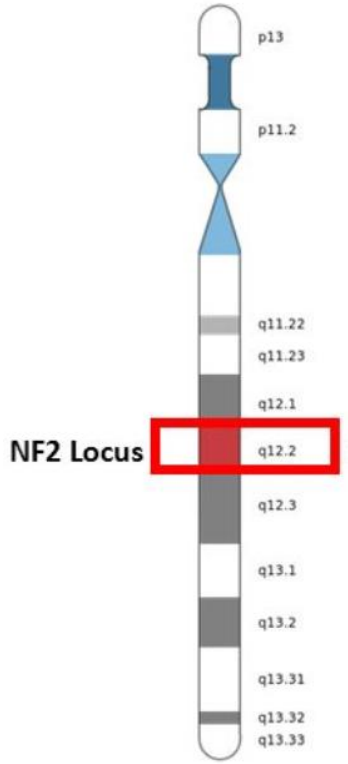


Ring Chromosome 22



Ring 22

22 r22



- Deletions occurs near the top of the chromosome and near the bottom of the chromosome
- The new “ends” join to form a circle or ***ring chromosome***
- Individuals with ring 22 are at increased risk of developing Neurofibromatosis type 2 (NF2)

What is Neurofibromatosis Type 2 (NF2)

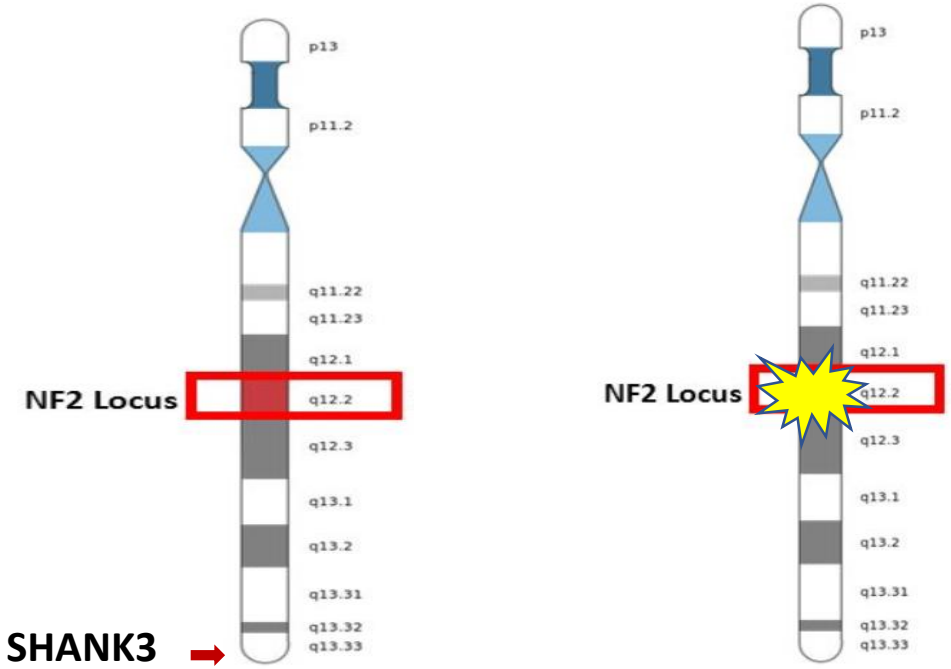
A genetic condition characterized by the growth of non-cancerous tumors in the nervous system

For example, tumors can occur on nerves carrying information from the inner ear to the brain leading to hearing loss, ringing in the ears, and loss of balance

Tumors can also occur elsewhere in the brain, spinal cord, and peripheral nerves

Two hits to develop NF2

- FIRST HIT
  - Cells can lose one copy of chromosome 22 because the ring is unstable in cell division - monosomy 22
- SECOND HIT
  - A pathogenic variant (mutation) can occur in the NF2 gene on the remaining copy of chromosome 22



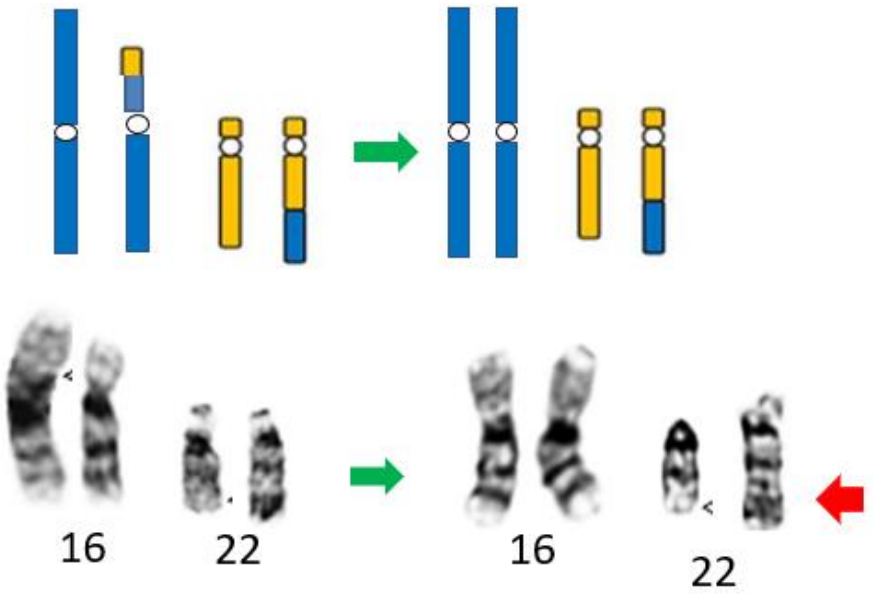
If your child has a terminal deletion by CMA, you don’t know if it is a ring or not

- Follow-up chromosome analysis (karyotype) is needed to determine if a ring chromosome is present.
- If your child has a deletion that is not caused by ring 22, the risk of NF2 is not increased.
- If your child has a pathogenic variant of SHANK3, the risk of NF2 is not increased.

Translocation

- Evidence of an unbalanced translocation – deletion of 22q13 and duplication of a second chromosome segment by CMA.
- Confirm by chromosome analysis.
- If translocation is present, test parents and other at-risk family members.
- In parent is a carrier, increased risk to other children and pregnancies.

- ***Translocations***



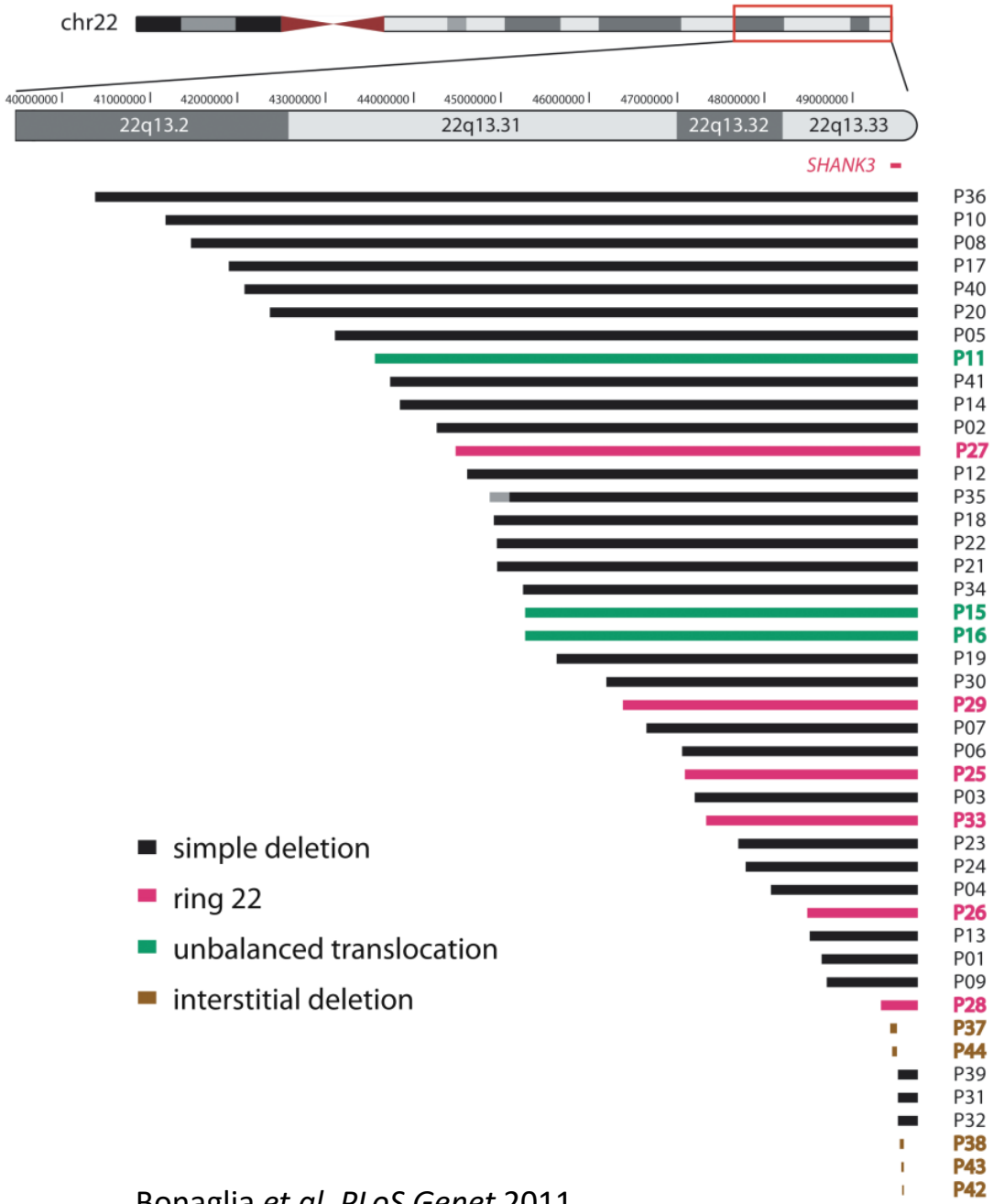
Unbalanced Translocation

- **May be inherited** from parent with balanced translocation
  - Parental studies are indicated if deletion of 22q13 and duplication of a second chromosome found on CMA
  - Can be inherited from either parent
- May be very difficult to detect if the involved segments are similar in size and staining pattern

CMA results – 44 Individuals

Deletion band 22q13.33 including *SHANK3*

- Variable deletion size (5kb-9Mb)
- No common breakpoints



Bonaglia *et al. PLoS Genet* 2011

Causes of PMS

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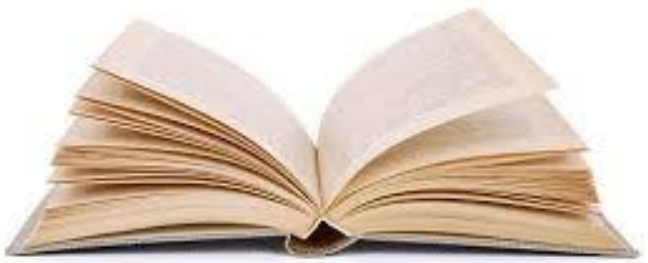
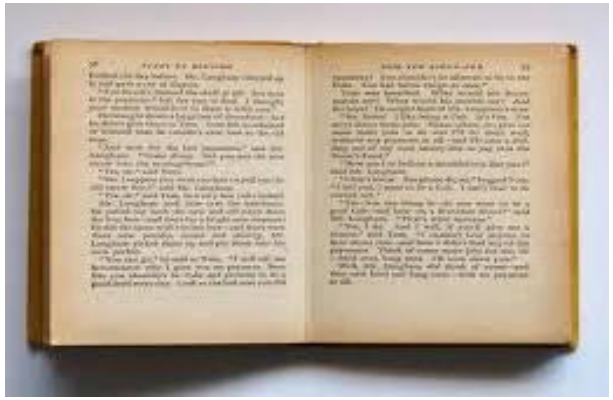
Pathogenic variants



Whole genome is like a book of instructions for our body

Each chromosome is a chapter is the book



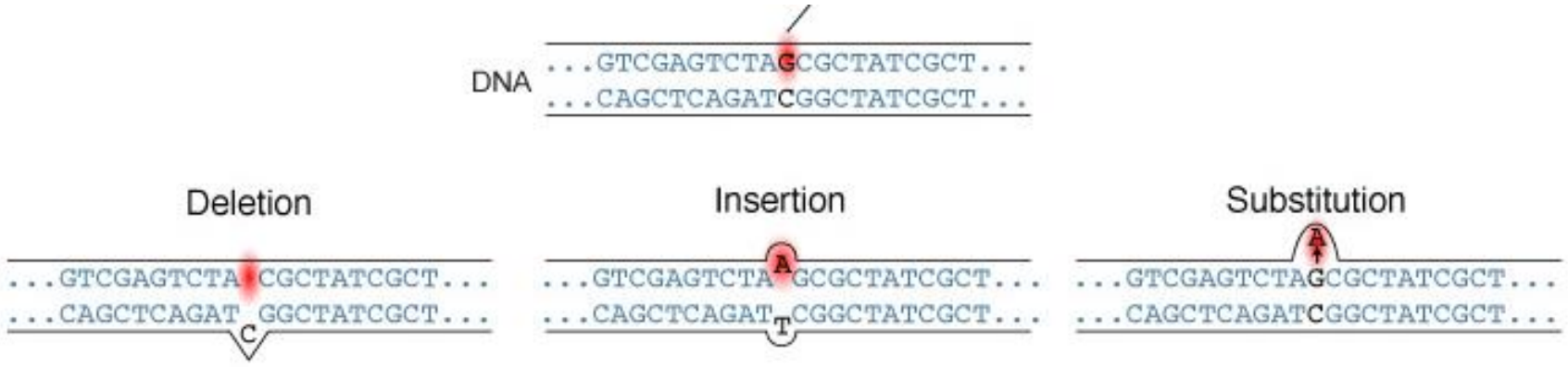
The genes are sentences in the chapters. The alphabet is A, T, G, C.

We are looking for misspelled words, missing words or paragraphs in the genome.

Pathogenic Variants of *SHANK3*

Sequence variants of *SHANK3*

- May affect 1 base or a few bases
- Detected by sequencing



Changes in the DNA

THE CAT ATE THE RAT
THE KAT ATE THE RAT Silent – the meaning is still the same; point mutation.

THE CAT ATE THE RAT
THE HAT ATE THE RAT Substitution – the sense of the sentence is changed; point mutation.

THE CAT ATE THE RAT
THE CAA TET HER AT Deletion – the sentence makes no sense; frameshift mutation.

THE CAT ATE THE RAT
THE ECA TAT ETH ERA T Insertion – the sentence makes no sense; frameshift mutation.

Interpretation or Comment

- Pathogenic variant in the *SHANK3* gene
  - May study parent to determine if variant is inherited or *de novo*
- Consistent with diagnosis of Phelan-McDermid syndrome
- Genetic counseling is warranted

Phelan *et al.*
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Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

Phelan-McDermid syndrome: a classification system after 30 years of experience

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Abstract

Phelan-McDermid syndrome (PMS) was initially called the 22q13 deletion syndrome based on its etiology as a deletion of the distal long arm of chromosome 22. These included terminal and interstitial deletions, as well as other structural rearrangements. Later, pathogenetic variants and deletions of the *SHANK3* gene were found to result in a phenotype consistent with PMS. The association between *SHANK3* and PMS led investigators to consider disruption/deletion of *SHANK3* to be a prerequisite for diagnosing PMS. This narrow definition of PMS based on the involvement of *SHANK3* has the adverse effect of causing patients with interstitial deletions of chromosome 22 to "lose" their diagnosis. It also results in underreporting of individuals with interstitial deletions of 22q13 that preserve *SHANK3*. To reduce the confusion for families, clinicians, researchers, and pharma, a simple classification for PMS has been devised. PMS and will be further classified as PMS-*SHANK3* related or PMS-*SHANK3* unrelated. PMS can still be used as a general term, but this classification system is inclusive. It allows researchers, regulatory agencies, and other stakeholders to define *SHANK3* alterations or interstitial deletions not affecting the *SHANK3* coding region.

Keywords: Phelan-McDermid syndrome, PMS, *SHANK3*, 22q13 deletion

Summary

- Phelan-McDermid syndrome is caused by a deletion of 22q13 or a pathogenic variant in the *SHANK3* gene
- The most common diagnostic test are chromosomal microarray (CMA) and gene sequencing
- Genetic counseling is always indicated to help families understand the results and to navigate the future