A Gathering:
For Persons Who Have TRP Syndromes
Sandusky, Ohio

The Genetic Basis of TRPS:
Perspectives and Current Research

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What is TRPS?
Common characteristics.

- Cone-shaped ends of the bones (epiphyses), especially in the fingers.
- Thin and/or sparse hair.
- Short stature or growth delay.
- Large and/or protruding ears.
- Eyebrows that are thick on inside and thin on outside.
- Thin upper lip and long philtrum (groove above lip).
- Round, bulbous nose.
- Bony growths or exostoses (always seen in TRPS).
- Learning difficulties (common only in TRPS2).

Other less common characteristics.

- General muscle weakness.
- Joint problems (pain, swelling, loose).
- Feeding and eating difficulties.
- Hip problems.
- Small hands and feet; bent fingers and toes.
- Loose, redundant, extra skin.
- Dental problems (missing, extra teeth).
- Small head and jaw.
- Speech difficulties.

What are the differences between TRPS I, II, and III?

TRPS I	TRPS II (LGS)	TRPS III
Coned finger joints	Coned finger joints	Coned finger joints
Short stature/Sparse hair	Short stature/Sparse hair	Short stature/Sparse hair
Thin upper lip, long philtrum, bulbous nose	Thin upper lip, long philtrum, bulbous nose	Thin upper lip, long philtrum, bulbous nose
Protruding ears, unusual eyebrows.	Protruding ears, unusual eyebrows.	Protruding ears, unusual eyebrows.
	Bony growths: exostoses	
	Cognitive and Learning difficulties common.	
		Severe shortening of hands and fingers

What are the risks of passing the bad TRPS gene to my children?

- TRP syndromes show a "Dominant" inheritance pattern.
- This means that, if you have a TRP syndrome, there is a 50% chance that your children will have the same syndrome.
- If neither you nor your spouse has a TRP syndrome, but you have a child with a TRP syndrome, then your chances of having another child with a TRP syndrome are very low (maybe 1 in 100,000).

What causes TRP Syndromes?

A genetic defect (mutation) in the TRPSI gene on one of the copies of chromosome 8 present in all of the cells of the body.

Genetics 101

- What is a cell?
- What is a chromosome?
- What is a gene?
- What is DNA
- What is a mutation?

What is a cell?

- The fundamental unit of life.
- All living things are made of cells.
- The human body is composed of trillions of cells.
- Cells group together in specialized ways to form tissues and organs.
- All cells share certain features that enable them to perform basic life functions.
- At the center of all cells is a nucleus that contains DNA (the genetic information storage component of the cell).

What is a Chromosome?

- These are the structures in the nucleus that contain the DNA.
- Each human cell has in the human body contains 46 chromosomes (23 from each parent).
- Each chromosome contains one, very long strand of DNA containing over a thousand genes.
- A gene is a segment of the Chromosome (DNA) that carries instructions for making a protein.

What is DNA made of?

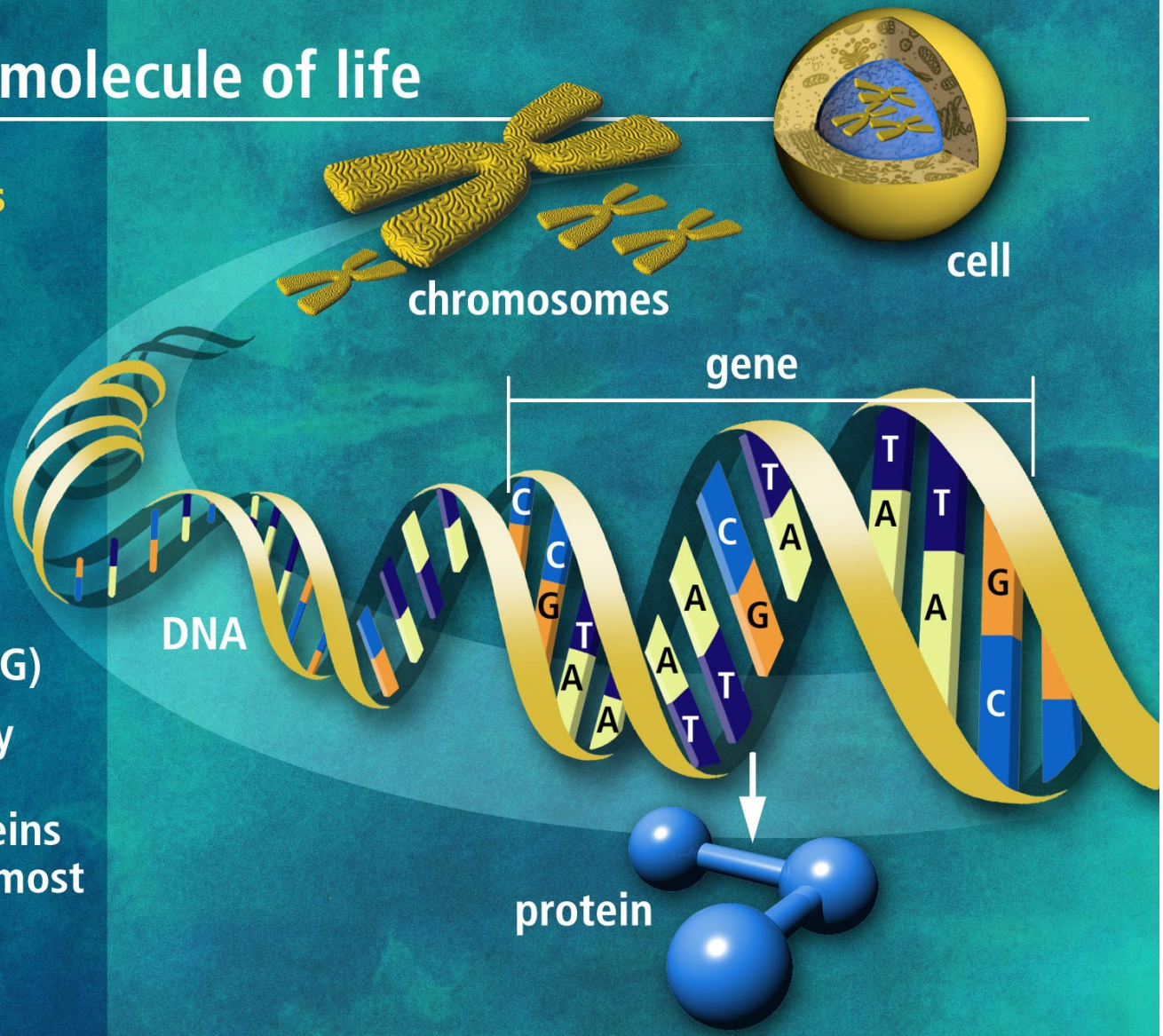
- DNA is a repeating polymer that contains 4 different chemical components.
- The 4 components are designated by their single letter abbreviations (A, C, G, T).
- An average gene contains several thousand letters.
- An average chromosome contains over 100 million letters.
- Each cell in the human body contains 3 billion letters (Actually 6 billion since each chromosome has a duplicate partner).
- The term genome refers to all of the DNA in all of the chromosomes of the cell.

DNA the molecule of life

Trillions of cells

Each cell:

- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions



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The genome as an encyclopedia.

- A simple way to think of the genome is like an encyclopedia.
- The "Encyclopedia Genome " would contain 46 (23 x 2) volumes, one for each chromosome.
- Each volume (chromosome) would contain over a thousand chapters (genes).
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- Each chapter (gene) would contain thousands of letters in a unique order using the 4 letters in the DNA alphabet (A, C, G, T).

The Language of DNA.

- The function of genes is to make proteins.
- In the language of DNA, all words are made up of 3 letters.
- A DNA sentence might read:

CAT ACT TAG GAG ATT TAT

- Each three letter word translates into a specific amino acid.
- Amino acids are the building blocks of proteins.

CAT ACT TAT GAG ATT TAG

His Thr Tyr Glu Ile Stop

DNA Genetic Code Dictates Amino Acid Identity and Order

DNA Sequence Is the Genetic Code.

GCA AGA GAT AAT TGT...

. . . Growing Protein Chain

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What is a mutation?

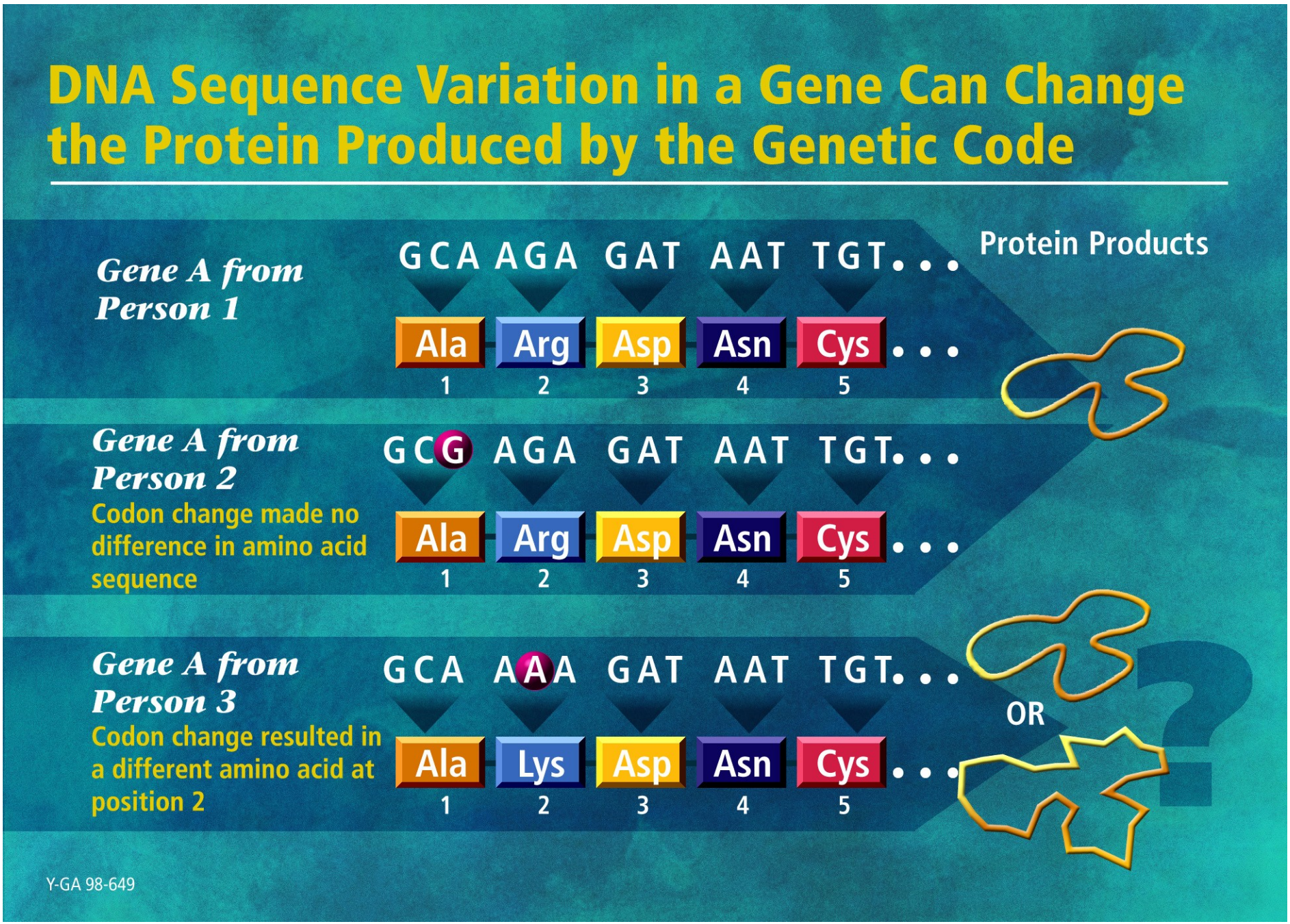
- A mutation is like a typographical error in the printing of the encyclopedia.
- It can be as simple as a single letter exchange (called a point mutation) or as complex as the deletion of several chapters in one of the volumes.
- The point mutations can be single letter substitutions, deletions, or insertions.

Point mutations.

Using the encyclopedia analogy, the point mutation is the smallest typographical error that can occur. It is the addition, deletion, or substitution of a single letter.

1. THE CAT DID EAT THE RED HAT.	**Normal**
2. THE RAT DID EAT THE RED HAT.	**Substitution (C to R)**
3. THE ATD IDE ATT HER EDH AT.	**1 base deletion (delete C)**
4. THE CHA TDI DEA TTH ERE DHA T.	**1 base addition (add H)**

DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code



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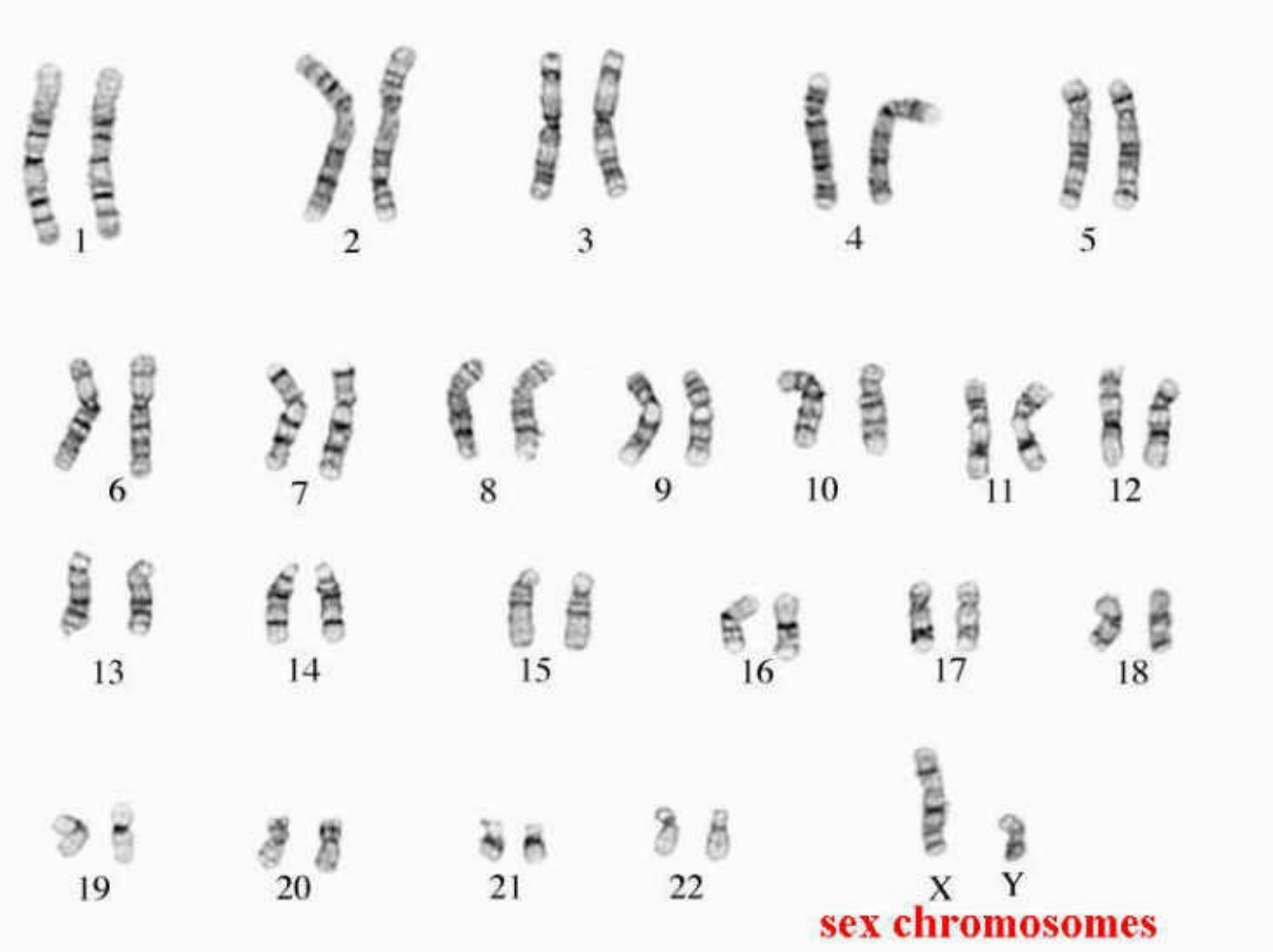
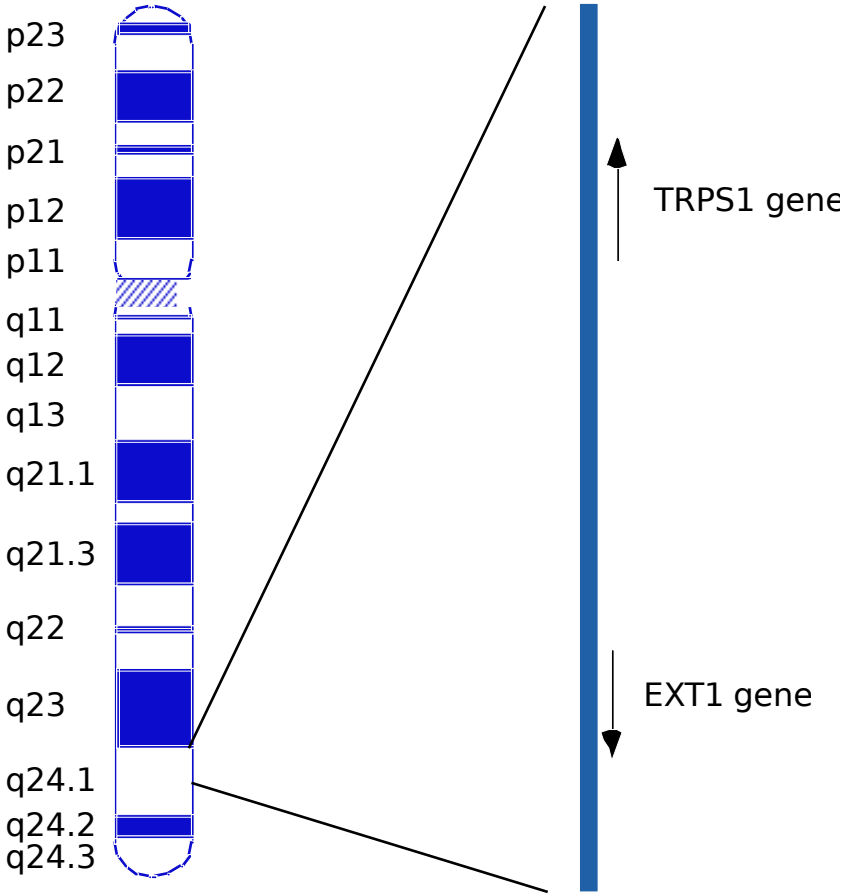
So what of TRP Syndromes?

- TRP syndromes are cause by mutations in a gene on chromosome 8.
- Chromosomes are numbered by size (Chromosome 1 is the largest).
- When chromosomes are treated with certain dyes, they show a specific banded pattern.
- The bands are numbered to provided scientists and physicians a point of reference.
- The location of TRPS mutations is centered on a specific region of chromosome 8 called: “8q24.1”

A Human Karyotype



Chromosome 8



Types of mutations that have been shown to cause TRP syndromes

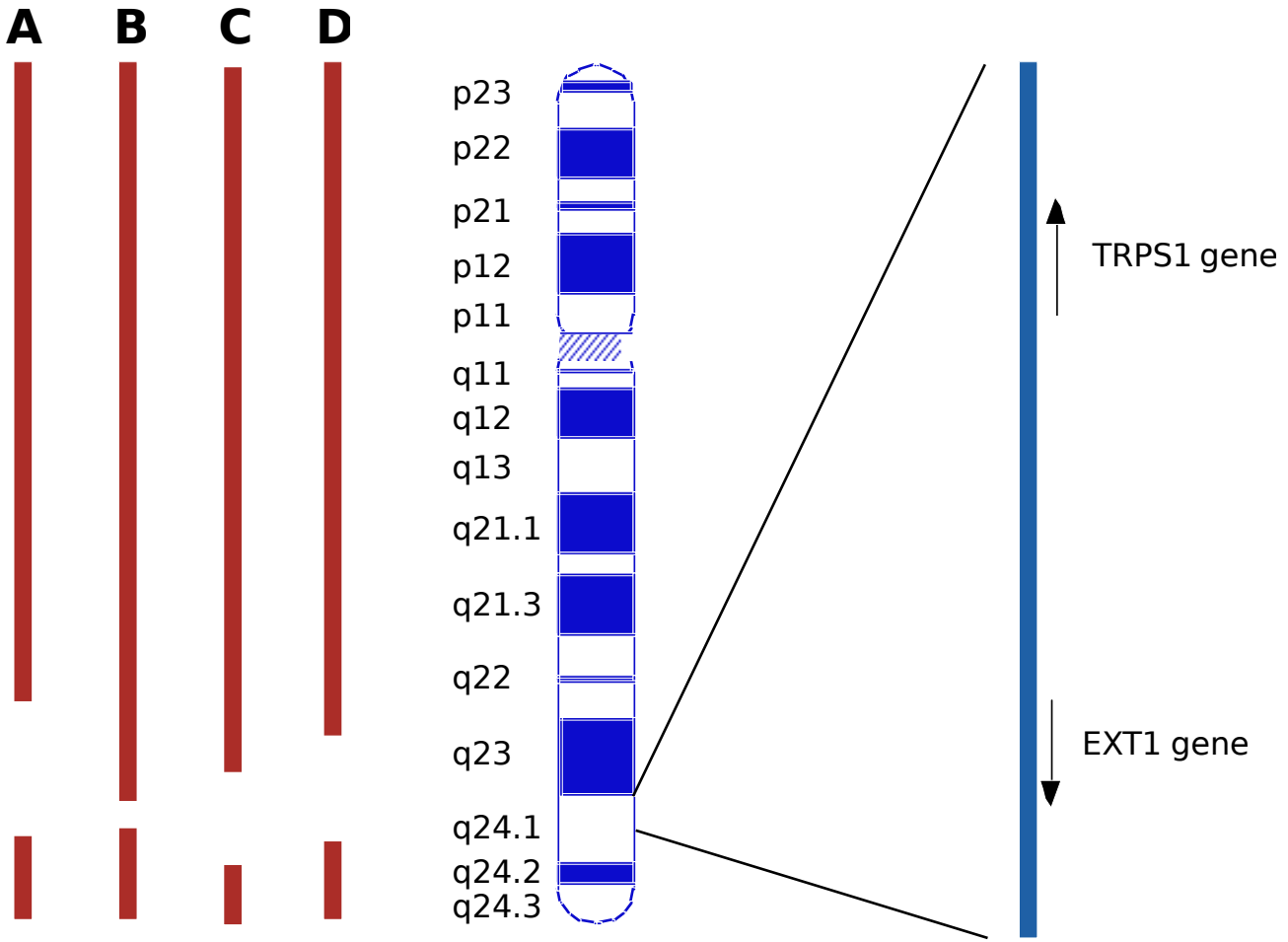
1. Chromosomal deletions and rearrangements involving 8q24.1.

2. Point mutations that cause an amino acid substitution resulting in a altered protein.

3. Point mutations that cause a shortened TRPS protein.

4. Point mutations that cause a scrambled and shortened TRPS protein.

Chromosomal deletions



Chromosomal Deletions

Remember Point mutations.

A point mutation is the smallest typographical error that can occur. It is the addition, deletion, or substitution of a single letter.

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Real DNA Point mutations.

The addition, deletion, or substitution of a single DNA letter (AGCT).

1. GTA CCG AGA GGC GCG TCA CTG AAA TGA **Normal**
   Valine Proline Arginine Glycine Alanine Serine Leucine Lysine Stop

2. GTA CCG AAA GGC GCG TCA CTG AAA TGA **Substitution (G-A)**
   Valine Proline Lysine Glycine Alanine Serine Leucine Lysine Stop

3. GTA CCG TGA GGC GCG TCA CTG AAA TGA **Substitution/Stop (A-T)**
   Valine Proline Stop

4. GTA CCG GAG GCG CGT CAT TGA AAT GA **Deletion (A) Frameshift**
   Valine Proline Glutamic Alanine Arginine Histidine Stop

5. GTA CCG AGC AGG CGC GTC ACT GAA ATG **Addition (C) Frameshift**
   Valine Proline Serine Arginine Arginine Valine Threonine Glutamic Methionine

Therefore TRPS Point mutations…..

1. Can cause an amino acid substitution resulting in a altered TRPS protein.

GTA CCG AAA GGC GCG TCA CTG AAA TGA

Valine Proline Lysine Glycine Alanine Serine Leucine Lysine Stop

2. Can cause a shortened TRPS protein.

GTA CCG TGA GGC GCG TCA CTG AAA TGA

Valine Proline Stop

3. Can cause a scrambled and shortened TRPS protein (Frameshifts).

GTA CCG GAG GCG CGT CAT TGA AAT GA

Valine Proline Glutamic Alanine Arginine Histidine Stop

What types of mutations are seen in TRPS I, II, and III?

TRPS I:

- Shortened Protein
- Frameshift- Scrambled and Shortened Protein
- Small chromosomal deletions

TRPS II (LGS):

- Large chromosomal deletions

TRPS III:

- Altered protein

How do mutations in the TRPS protein cause the characteristics seen in TRPS individuals?

- **This is the big question that scientists are currently asking…**
- **To answer it we must first determine the normal function of the TRPS1 protein.**

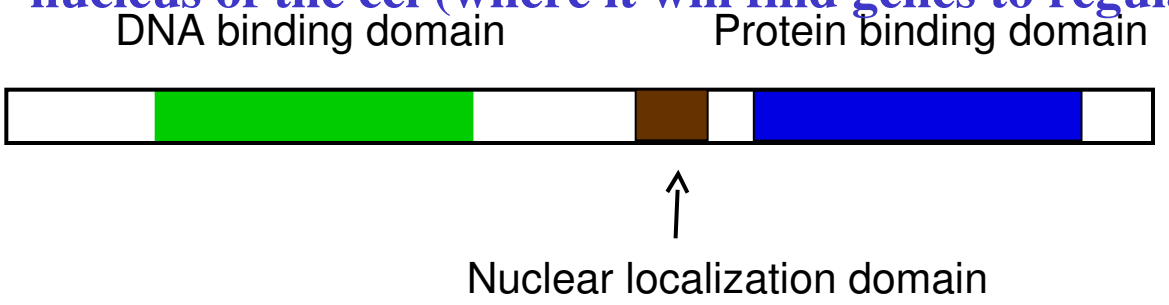
What is the function of the TRPS1 protein?

- The function of the TRPSI protein is still largely unknown.
- But clues to its function have come from the analysis of its structure and organization.
- It has similarities to a class of proteins that helps regulate the expression of "third party" genes, "Transcription Regulators".

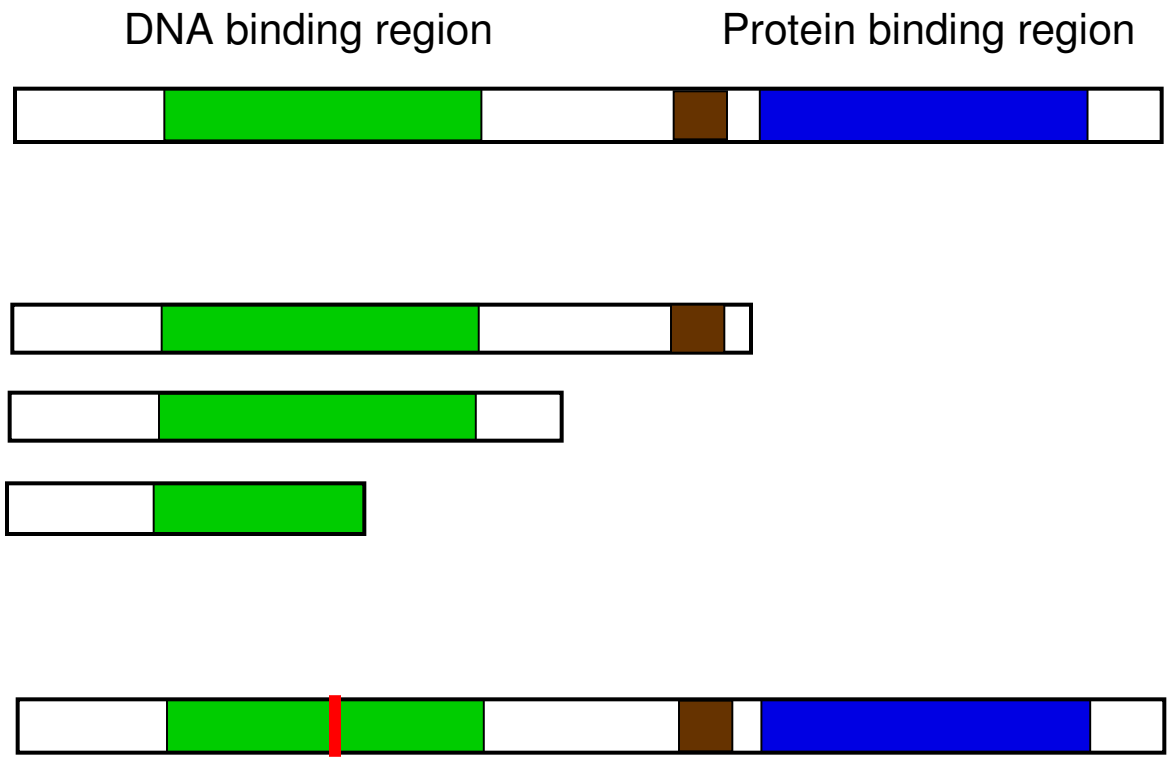
What is the structure of the TRPSI gene?

The TRPSI proteins seems to have at least three functional regions or "domains".

1. A DNA binding domain that appears to be able to bind to DNA sequences in front of other "third party" genes.
2. A Protein binding domain that seems to be able to bind to to itself and other proteins to form multi-protein complexes.
3. A nuclear localization domain that tells the protein to go to the nucleus of the cel (where it will find genes to regulate).



Structure of the TRPS1 normal and mutant proteins?



A model for how normal and mutant proteins work.