Behind the letters: A guide to understanding your genetic test results

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Outline

BASICS OF GENETICS

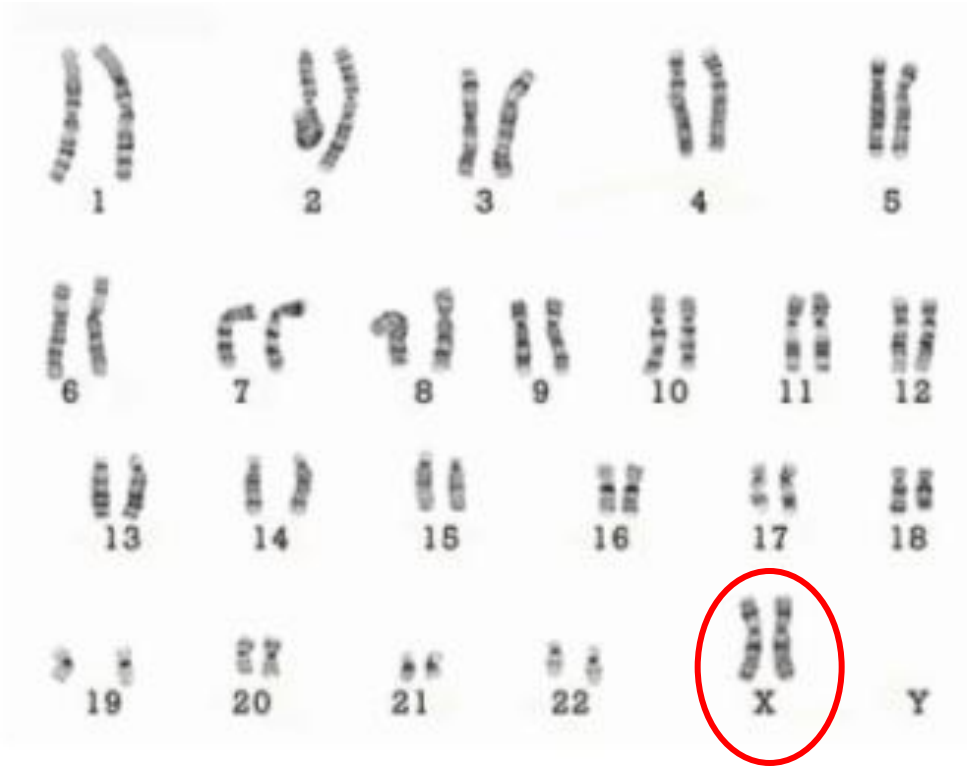
GENETICS OF NOONAN SYNDROME

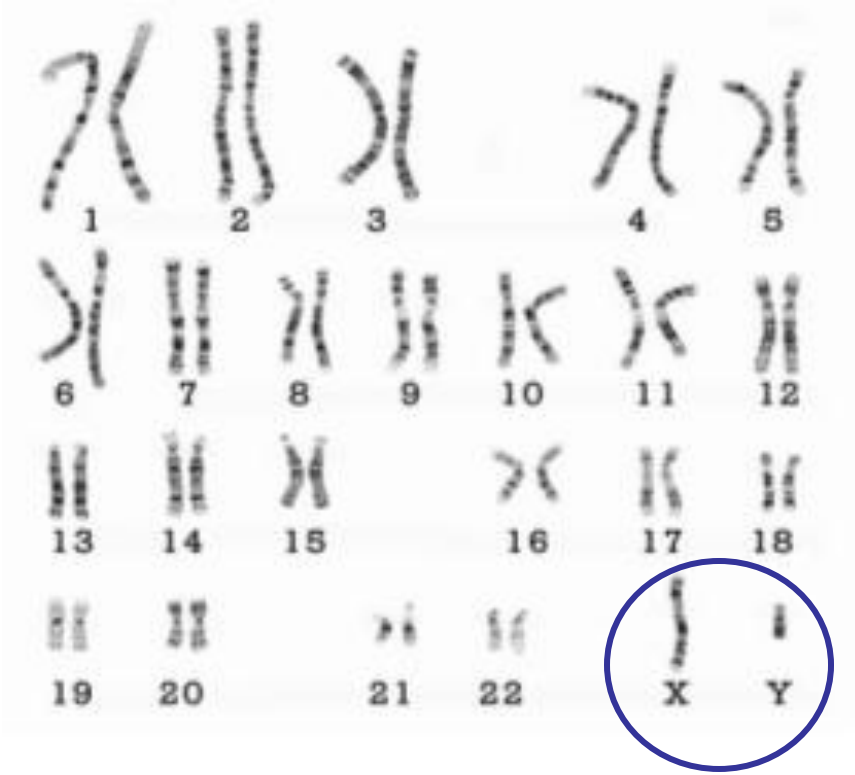
GENETIC TESTING OPTIONS

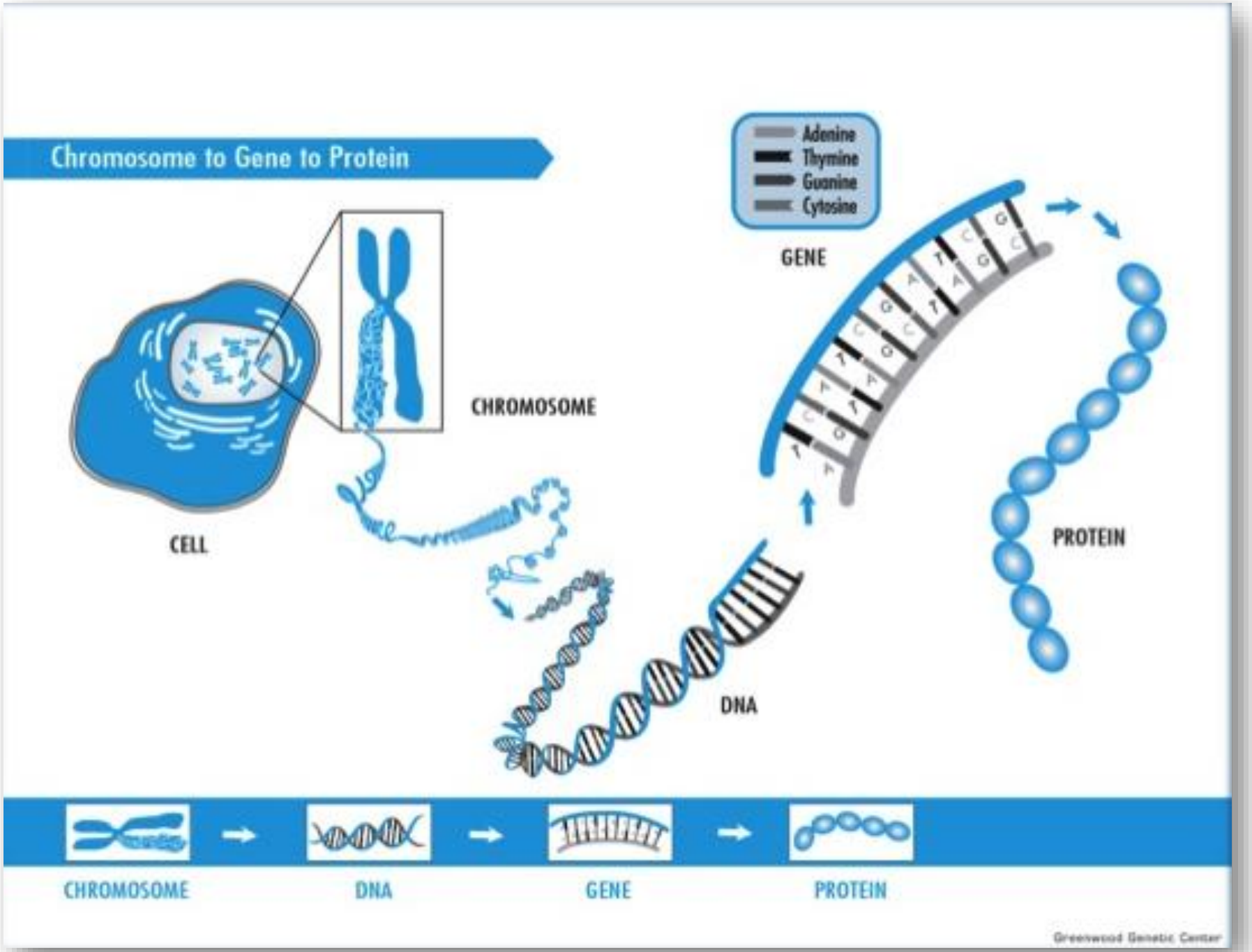
UNDERSTANDING YOUR GENETIC TEST RESULTS

FREQUENTLY ASKED QUESTIONS

Chromosomes

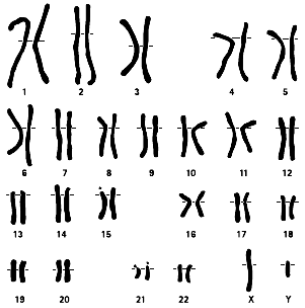





Chromosome to Gene to Protein
Adenine
Thymine
Guanine
Cytosine
GENE
CHROMOSOME
CELL
DNA
PROTEIN
CHROMOSOME
DNA
GENE
PROTEIN
Greenwood Genetic Center

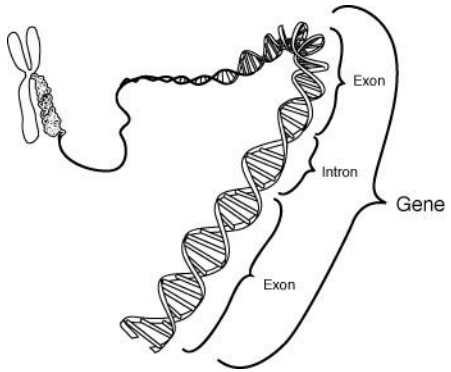
Genetics

Genome



Chromosome

Gene



DNA – A, C, T, G

Enclyclopedia

Volume

Sentence

Alphabet- A, B, C, D…

Genetics of Noonan syndrome

Gene	Percentage of individuals with NS
*PTPN11**	50%
SOS1	10-13%
LZTR1	~8%
*RAF1**	5%
RIT1	5%
SOS2	~4%
*KRAS**	<5%
MRAS	<1%
NRAS	<1%
RRAS2	<1%
*BRAF**	<2%
Others (*SHOC2*, *PPP1CB*…)	Unknown

*gene can cause other conditions

Genetic variants

- Variants are changes in a gene.
- We ALL have genetic variants in our genes – they are what make us unique!
- Some changes are “benign” and do not cause any problems.
- Some changes are more serious and can cause problems with what that particular gene is supposed to do.
  - These are often called “Pathogenic” variants.

Types of variants

Original

THE CAT HAD RED FUR AND RAN FAR.

Deletion

THE CAT HAD RED FUR AND RAN FAR.

THE CAT HAR EDF URA NDR ANF AR.

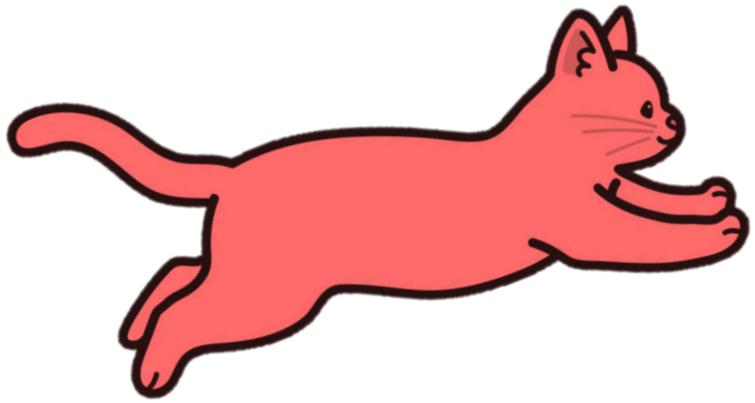
Missense

THE CAT HAD RED FER AND RAN FAR.

THE MAT HAD RED FUR AND RAN FAR.

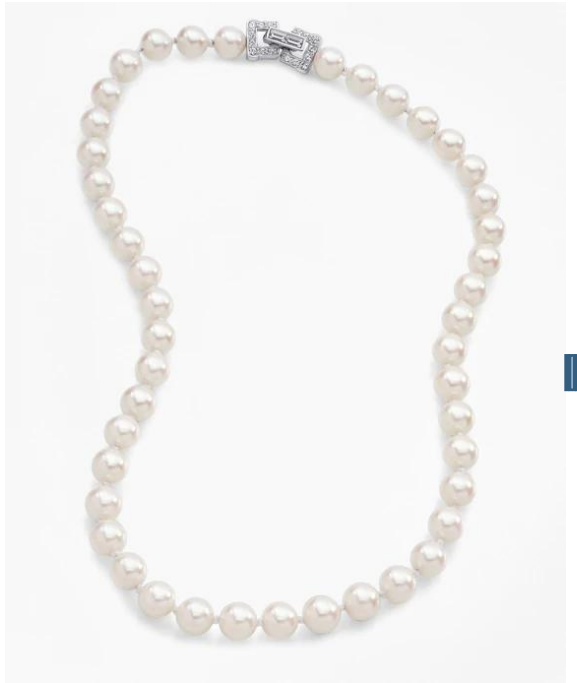
Nonsense

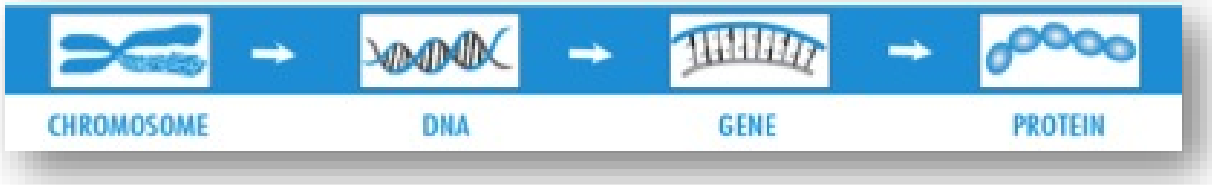
THE CAT HAD RED. 



Types of variants in Noonan syndrome

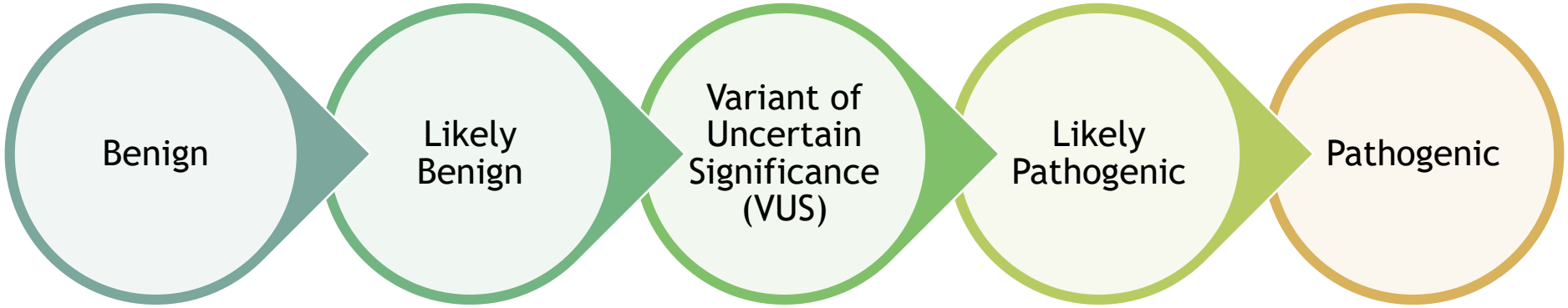
- Many of the variants that cause NS are misspellings in the genes.
- The variant changes an amino acid (bead).
- This change causes the gene to code for a protein that is different than the original protein.
- This change affects the ability of the protein to work correctly.





Variant classification

- Genetic testing laboratories will classify variants along the following spectrum:



Benign vs. Pathogenic

- Often times, the lab may be able to predict if a change in a gene is likely to be benign or pathogenic IF:

- The specific change has been seen before in other children with the condition OR

- If the specific change has been seen before in healthy, unaffected individuals or their parents.

Variants of unknown significance (VUS)

- If a gene change is found but has NOT been seen before or reported in the medical literature, then it can make it very hard to interpret the results.
- These are called "variants of uncertain significance" (VUS)

- Testing other family members may help us interpret the results.
- If a parent or unaffected sibling has the same change, then it is probably benign.
- If neither parent has the same change, then it might be pathogenic.

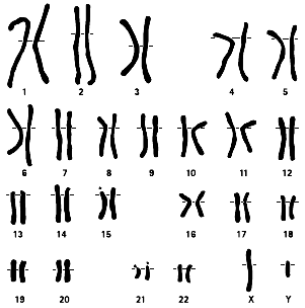
How to interpret a VUS

- Familial testing – does the variant segregate with the phenotype/condition?
- Software prediction programs – can give predictions about the effect of the variant on the gene function/protein
- Conservation studies – Is the location of the variant highly conserved across different species?
- Population databases– has this specific variant been seen in "healthy" populations and if so, with what frequency?

Genetic Testing Options

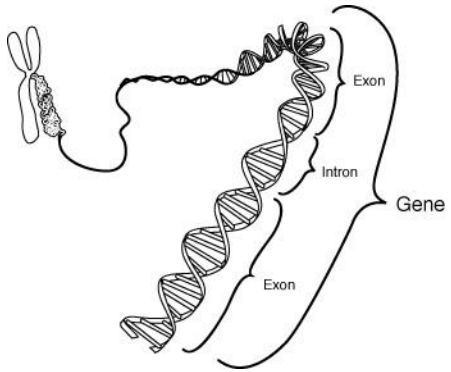
Genetics

Genome



Chromosome

Gene



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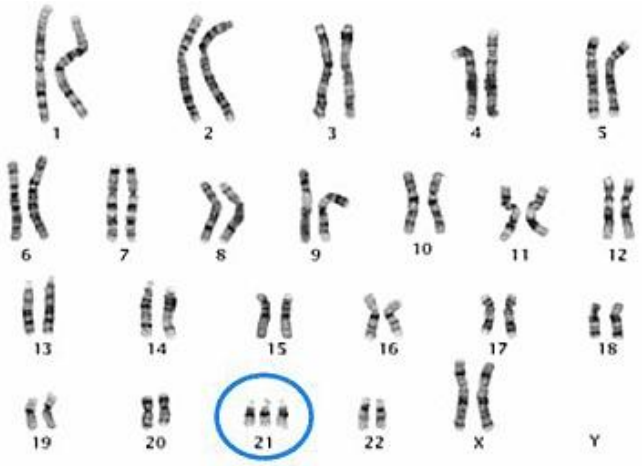
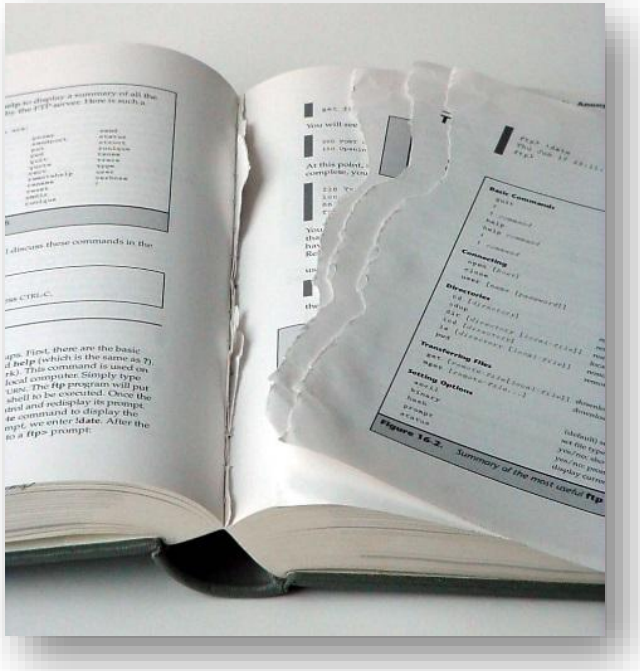
Chromosome Analysis

- Chromosome analysis involves looking at all of the chromosomes under a microscope.
- Looking for extra or missing entire chromosomes or large pieces of chromosomes.
- Example: Down syndrome (trisomy 21)
- Limitations: Can only detect relatively LARGE chromosome abnormalities, but will miss smaller ones.



Chromosome microarray analysis (CMA)

- Chromosome microarray analysis is a computer technique that analyzes a person's DNA to a reference DNA.



- It is able to detect very small missing or extra pieces of chromosome material.

- We are able to see much more detail than a routine chromosome study.

Single Gene Testing

- Single gene testing involves sequencing/reading a single gene and looking for variants (i.e. misspellings) in any of the letters.
- You have to know your gene of interest

Human brian is still evolving, says scientist

THE human brain is still evolving, scientists said today.

Researchers at the University of Chicago have identified two genes linked to brain size which are rapidly evolving in humans.

man evolution — the growth of brain size and complexity — is likely still going on.

"Meanwhile, our environment and the skills we need to survive in it are changing faster then we ever

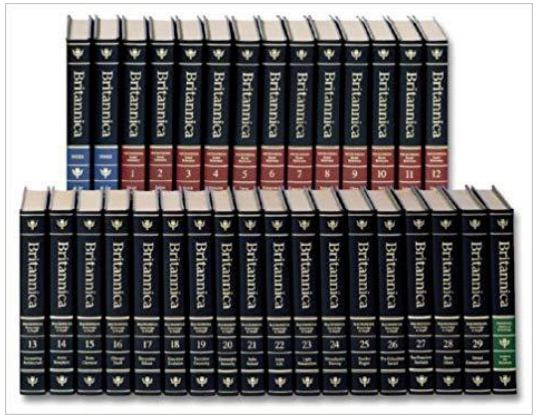
Multi-Gene Panel Testing

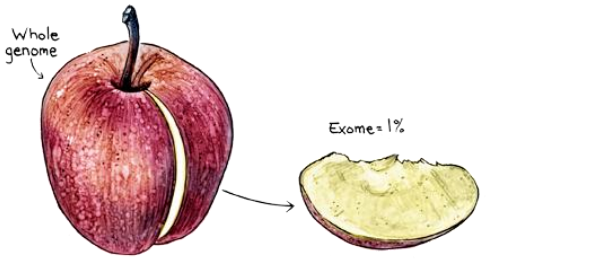
- Often times, genetic conditions are caused by more than one gene.
- Multi-gene panels involve looking at 3-100+ genes
- Identify misspellings in any of those genes that may cause the condition.

Genes	A2ML1, ACTB, ACTG1, BRAF, CBL, HRAS, KAT6B, KRAS, LZTR1, MAP2K1, MAP2K2, NF1, NRAS, NSUN2, PPP1CB, PTPN11, RAF1, RASA1, RASA2, RIT1, RRAS, SHOC2, SOS1, SOS2, SPRED1

Exome sequencing (ES)

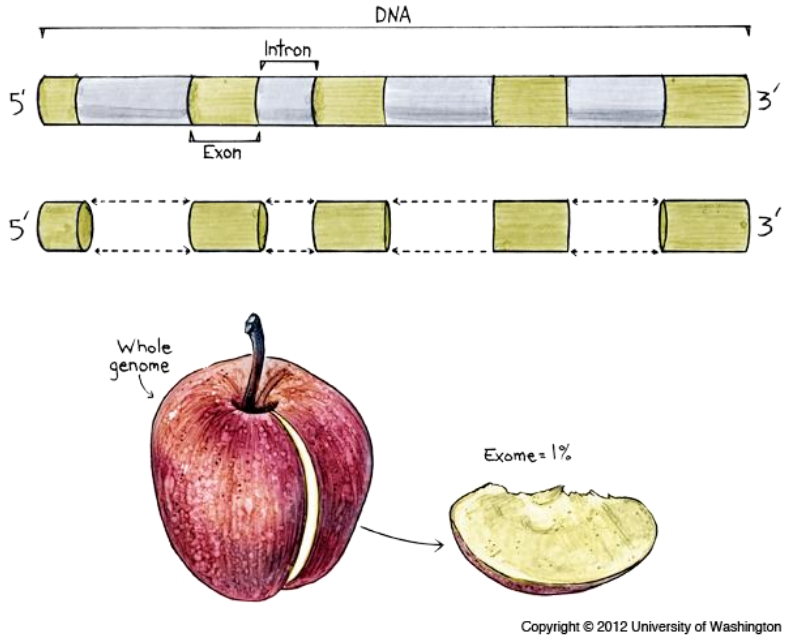
- Whole exome sequencing examines the coding parts (exons) of all of our genes.
- Interpretation can be difficult if we identify variants with unknown/ uncertain significance OR in genes that have not been associated with a syndrome yet.
- The likelihood of getting an “answer” is 30-40% depending on the patient population and indication





Genome sequencing (GS)

- Whole genome sequencing examines the coding AND non-coding parts of our entire genome.
  - 3.2 ***billion*** base pairs
- It also has the ability to detect chromosome deletions and duplications, similar to a chromosome microarray analysis, mitochondrial DNA, and other conditions.
- Insurance coverage is improving
- Interpretation can be difficult given the uncertainty of the types of results that may be uncovered.
- Great potential as a first tier test for individuals with suspected genetic conditions.



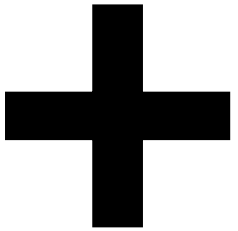
Genetic testing for Noonan syndrome

- Individuals may be diagnosed by:
- Panel testing for: Rasopathies, developmental delay, congenital heart defects, cardiomyopathy
  - Would need to make sure that the genes for NS are on the list of genes being tested
- Whole exome/genome sequencing
- Known familial variant testing
  - This is used *only if* the variant in the family is already known and a family member wants to get testing for that condition only.

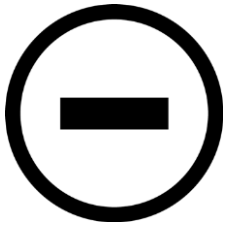
Understanding your genetic test result

Genetic test results may come back:

- Positive - meaning that a known disease-causing (pathogenic) variant was identified



- Negative – no disease-causing variants were identified at this time



- Variant of uncertain significance

Non-diagnostic test results

- If results are NEGATIVE or with a VUS this does NOT necessarily mean that you/your child does not have Noonan syndrome.
- They could still have NS or a Rasopathy, but we just have not identified the specific genetic cause yet.
- The genetic test may come back with a variant that has not been previously reported in the literature or in databases.
  - This could mean that the change is rare or unique in your family OR there may be other individuals with the same change, who have just not been reported in the medical literature.
- If more than one variant is identified on the genetic test, further discussion with a genetics provider is needed to help interpret the significance of each finding.

Sample Exome Report

Result: Positive

- Causative variant(s) in disease genes associated with reported phenotype: **POSITIVE**
- Variant(s) in disease genes possibly associated with reported phenotype: **SEE INTERPRETATION**
- ACMG Secondary Findings: **None Identified**

Causative Variant(s) in Disease Genes Associated with Reported Phenotype:

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Inherited From	Classification
PTPN11	PTPN11-related RASopathy	Autosomal Dominant	c.417 G>C p.(E139D)	Heterozygous	De Novo	Pathogenic Variant

Understanding genetic test results

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Nucleotide #	1 2 3	4 5 6	7 8 9	10 11 12	13 14 15	16 17 18	19 20 21	22 23 24	…	417
Gene:	THE	CAT	HAD	RED	FUR	AND	RAN	FAR…		ANP
Amnio acid #	1	2	3	4	5	6	7	8	…	139

- "c.417G>C" means at position number 417 in the DNA code (c.DNA), the nucleotide "G" was changed to an "C"
- "p.E139D" means that amino acid number 139 in the protein chain, the amino acid Glutamic acid (E) was change to Aspartic acid (D). *May also be written Glu139Asp

Understanding genetic test results

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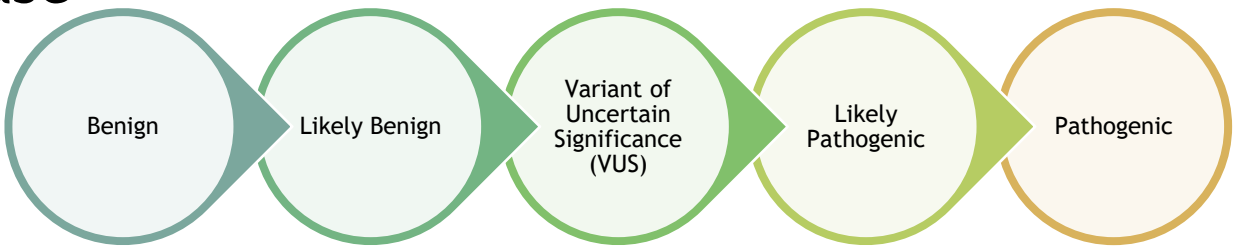
- Heterozygous = one variant was identified on one copy of the gene
- De Novo = “anew” Not inherited from either parent.
- Pathogenic = causes the condition/disease

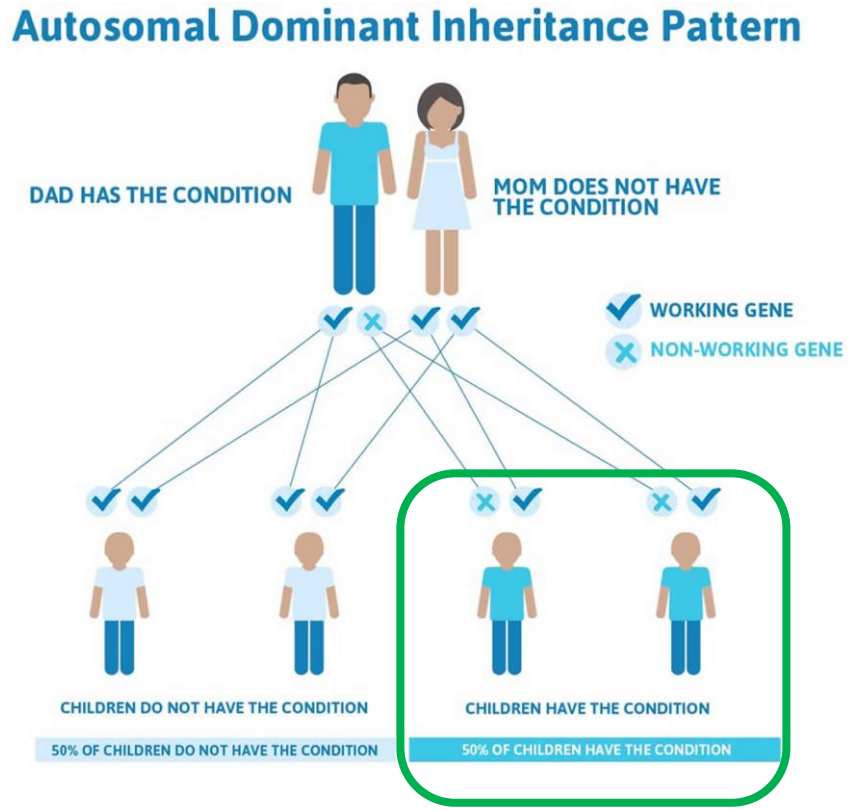


Frequently asked questions

What are the chances of having another child with NS?

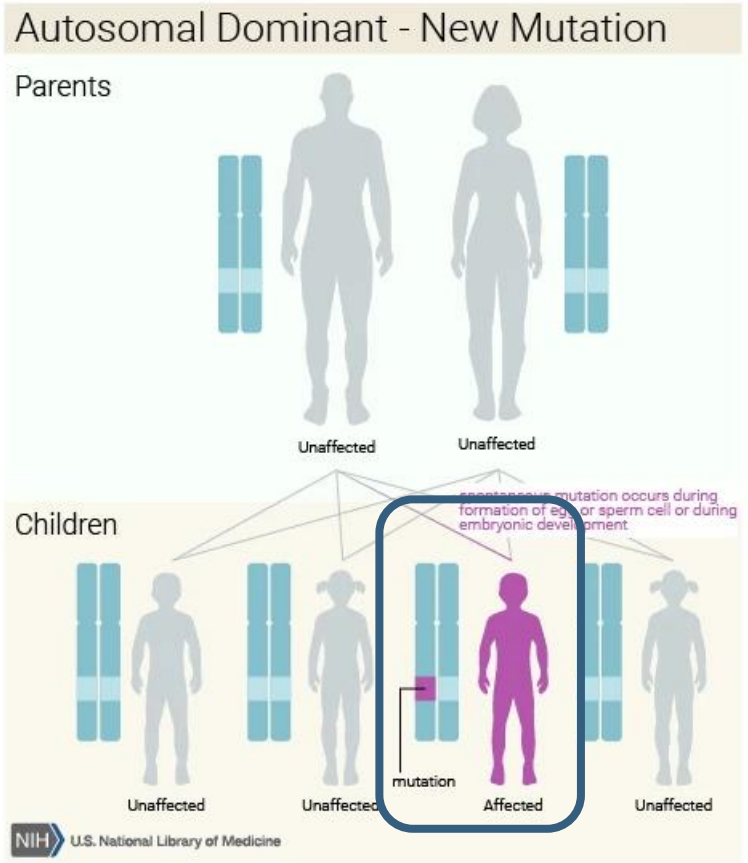
- Noonan syndrome is most often inherited in an autosomal dominant manner.

- If a parent has NS, there is a 50% chance of having a child with NS or 50% chance of passing it on *with each pregnancy*



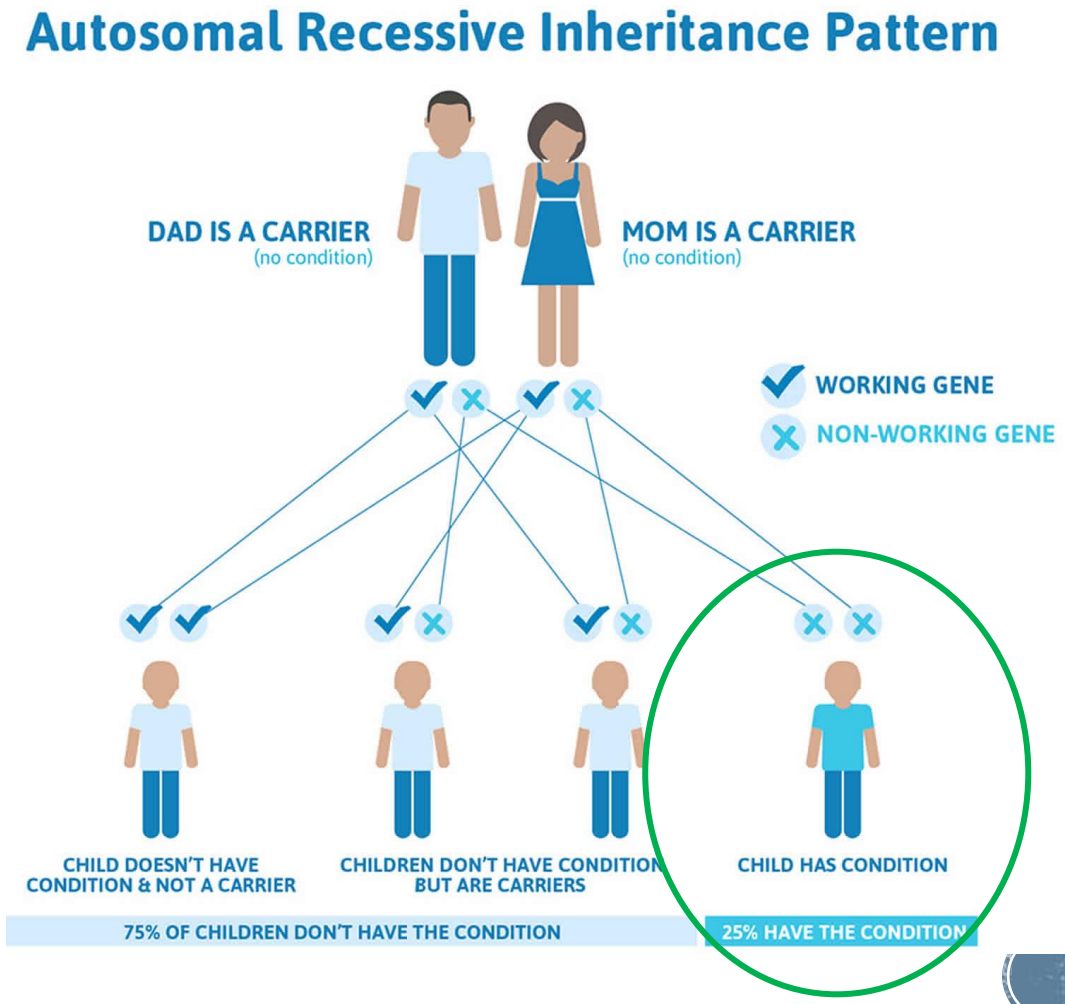
What are the chances of having another child with NS?

- If the parent does NOT have NS, the chances of having another child with NS are very low (less than 1%)
- Rarely, the parent may carry the genetic change in a small percentage of their cells. This is called mosaicism.
  - If the egg or sperm cells carry the genetic change, there is an increased chance of having a child with NS, even if the parent is unaffected.
  - This is difficult to detect, but also very rare.



LZTR1-related Noonan syndrome

- LZTR1-related NS can be inherited in a dominant OR recessive manner.
- If recessive, both parents are *carriers* of the condition.
- Carriers are typically unaffected.
- If both parents are carriers of the same condition, there is a 25% (1 in 4) of having a child with the condition.



Why is genetic testing important?

- Sometimes knowing the genetic variant ("genotype") may help predict the clinical features that may be more likely to occur in an individual ("phenotype").
  - Examples: heart features (PS vs HCM), development, growth, seizure risk
- But there remains significant variability both between and within families/individuals who may carry the same gene and same variant, so we need to be cautious with making assumptions and predictions.
- Knowing your specific gene and variant may impact management recommendations or closer surveillance of certain features.

Are other family members at an increased risk of having a child with NS?

- No, unless other family members also have NS. The risk for anyone in the general population to have NS is around 1 in 1,000 to 1 in 2,500.

- If an individual has NS, then the risk to their children would be 50%.

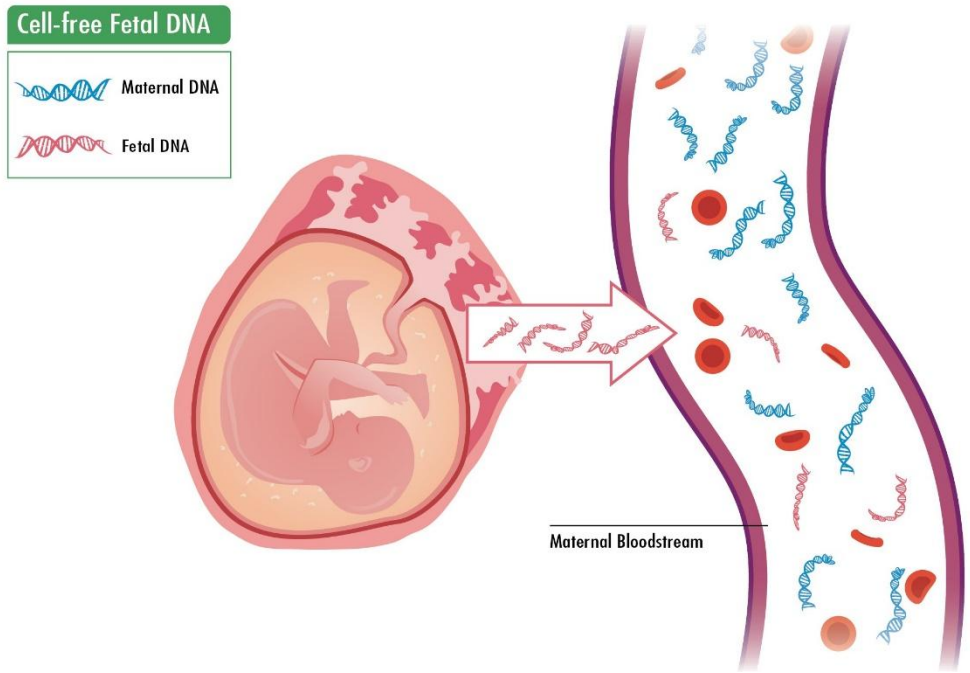
- If it is autosomal recessive LZTR1-related NS, then other family members may be *carriers* of the condition. They can be offered carrier screening for NS (and many other conditions).

What reproductive options are available in future pregnancies?

- Recommend genetic counseling *before* getting pregnant to discuss options (preconception counseling)
- The recurrence risk if it was not inherited is low, but some couples may want to pursue genetic testing.
- In-vitro fertilization (IVF) with preimplantation genetic testing (PGT)
  - This involves the couple going through IVF, testing the embryos for the genetic condition, and implanting the embryos that do not carry the genetic change.
- Prenatal Diagnosis
  - CVS (chorionic villi sampling) –first trimester
  - Amniocentesis – second trimester
- Need to know the specific genetic variant you are testing first!

Non-invasive Prenatal Testing

- NIPT is a blood test that is done on the mother that tests the fetal DNA.
- This is most commonly used to screen for chromosome abnormalities, such as Down syndrome, but can now also screen for conditions such as Noonan syndrome **if asked for specifically**
- This test is not useful if the MOTHER has NS because the test cannot differentiate between the maternal DNA and fetal DNA if a variant is detected.
  - It CAN be used if the father has Noonan syndrome or if neither parent has Noonan syndrome.



When in doubt…

- Ask your genetics providers!
- National Society of Genetic Counselors
  - www.nsgc.org
- American College of Medical Genetics
  - www.acmg.net

Thank you!

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Noonan syndrome Walk
San Antonio, TX (2014)