# DBA Genetics 101

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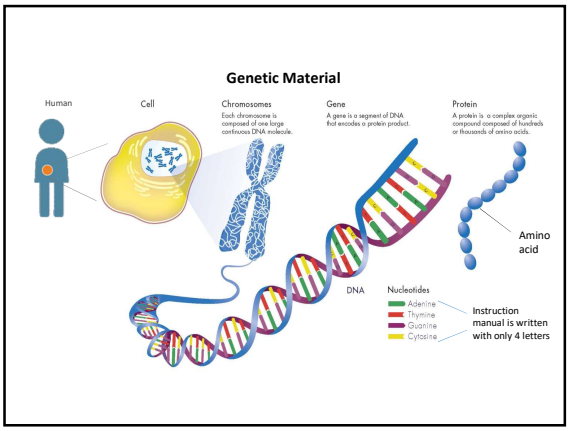
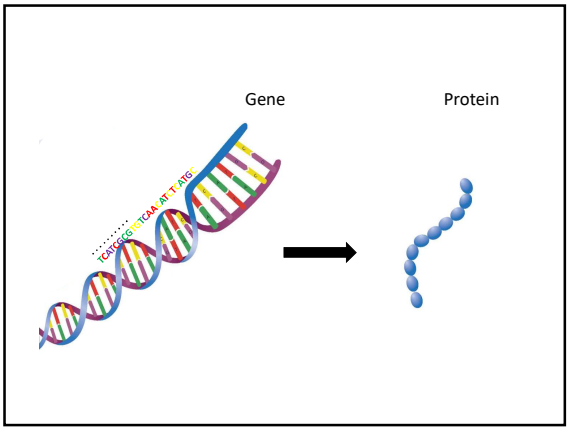


Gene

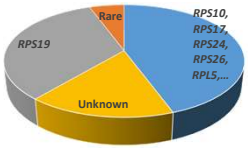
Protein

ACTGGTCACTCATCGCGTGTCAACATCTCATG
GTCAACATCTCATGCTGGTCACTCATACTGGTC
ACTCATAACATCTCATGCGTCAACATCTCGTCA
CTCATACACTGGTCACTCATCGCGTGTCAACAT
CTCATGCGTCAACATCTCATGCTGGTCACTATG
CTGGTCACTCATACTGGTCACTCATAACATCTC
ATGCGTCAACATCTCGTCACTCATACACTGGTC

## Genes & proteins associated with DBA

| GENE | PROTEIN |
|---|---|
| *RPL5* | Ribosomal protein L5 |
| *RPL11* | Ribosomal protein L11 |
| *RPL35A* | Ribosomal protein L35A |
| *RPS10* | Ribosomal protein S10 |
| *RPS17* | Ribosomal protein S17 |
| *RPS19* | Ribosomal protein S19 |
| *RPS24* | Ribosomal protein S24 |
| *RPS26* | Ribosomal protein S26 |

| Gene | % of DBA Attributed to Gene |
|---|---|
| *RPS19* | 30% |
| *RPS10* | 40% |
| *RPS17* | |
| *RPS24* | |
| *RPS26* | |
| *RPL5* | |
| *RPL11* | |
| *RPL35A* | |
| *RPS7, RPS15A, RPS20, RPS27, RPS28, RPS29* | Rare |
| *RPL15, RPL17, RPL18, RPL19, RPL26, RPL27, RPL31, RPL35* | |
| *TSR2, GATA1* | |



Normal RPS19

..... ATCGGTAATTCATCGCGTGTCAACATCTCATGCCGTT ....

Normal ribosomal protein S19

Mutated RPS19

..... ATCGGTAATTCATCGCGTGTCAACATCTCATGCCGTT ....

Abnormal ribosomal protein S19

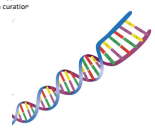

## How do we test for gene mutations that cause DBA?

- Gene panels
  - Testing multiple genes simultaneously
  - All panels are not created equal
  - If your genetic testing was negative, you will need testing again if:
    - New DBA genes are discovered
    - Enhanced testing technology has improved detection of mutations that previous testing may have missed
    - Previous testing only included detection of certain types of mutations
  - If your genetic testing is positive for a mutation in a DBA gene, additional testing is not necessary for you (even if new genes are discovered)

| LabA | | LabB | LabC |
|---|---|---|---|
| *RPS10* | *RPS28* | *RPS10* | *RPS10* |
| *RPS17* | *RPS29* | *RPS17* | *RPS17* |
| *RPS19* | *RPL15* | *RPS19* | *RPS19* |
| *RPS24* | *RPL17* | *RPS24* | *RPS24* |
| *RPS26* | *RPL18* | *RPS26* | *RPS26* |
| *RPL5* | *RPL19* | *RPL5* | *RPL5* |
| *RPL11* | *RPL26* | *RPL11* | *RPL11* |
| *RPL35A* | *RPL27* | *RPL35A* | *RPL35A* |
| *RPS7* | *RPL31* | *GATA1* | |
| *RPS15A* | *RPL35* | *RPS15A* | |
| *RPS20* | *TSR2* | *RPS20* | |
| *RPS27* | *GATA1* | *TSR2* | |

## How do we test for gene mutations that cause DBA?

- Whole exome sequencing (WES) or whole genome sequencing (WGS)
  - Testing ALL genes simultaneously, not just those known to cause DBA
    - >20,000 genes in our genome
    - More likely to be research based
    - May not detect all types of mutations
    - Phenotype driven curation



+20,000

ACTGGTCACTCATCGCGTGTCAACATCTCATGCGTCAACATCTCATGCTGGTCACTCAT
ACTGGTCACTCATAACATCTCATGCGTCAACATCTCGTCACTCATACACTGGTCACTCA
TCGCGTGTCAACATCTCATGCGTCAACATCTCATGCTGGTCACTATGCTGGTCACTCAT
ACTGGTCACTCATAACATCTCATGCGTCAACATCTCGTCACTCATACACTGGTCACTCA
TA

## What is WES/WGS?

- In WES, only the exons are sequenced
  - Exons are regions of the gene that contain the instructions for creating the protein
  - Mutations are most often found in exons
  - Exons make up only ~2% of a gene
- In WGS, almost the entire gene (introns and exons) is sequenced
  - Introns are regions of the gene that regulate the protein coding sequence

ATCGGTAATTCATCGCGTGTCAACATCTCATGCCGTTATCGGTAATTCATCGCGTGTCAACA

exon intron exon

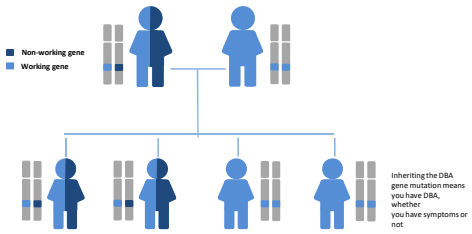
## Why is it important to identify your DBA gene mutation?

- Reproductive options
  - Prenatal diagnosis
  - IVF/PGD (preimplantation genetic diagnosis)
- Future gene therapies
- Learning new genotype/phenotype correlations
- Inheritance pattern – chance of passing it on to offspring

## How is DBA inherited?

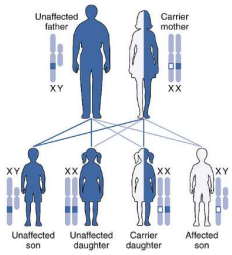
- Autosomal dominant or X-linked recessive, depending on the causative gene
  - RP genes are inherited in an autosomal dominant pattern
  - GATA1 and TSR2 are inherited in an X-linked recessive pattern
- 55-60% of DBA cases are not inherited, instead the mutation occurs brand new in the patient (*de novo*)
  - Siblings aren't at risk, but patient can pass on to their children

## Autosomal Dominant Inheritance




Each child has a 50% chance of inheriting the DBA gene mutation

## X-linked Recessive Inheritance




Each son has a 50% chance of having DBA
Each daughter has 50% of being a carrier (carriers do not have DBA)


**Questions?**