RARE ENTREPRENEUR BOOTCAMP

Genetic Diagnosis

April 2023

Paul Kruszka, MD, MPH, FACMG
Chief Medical Officer, GeneDx
pkruszka@genedx.com

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CONTENTS

- Introduction
- Genetic terminology
- Genetic testing
- The diagnostic odyssey
- Finding your group
- The next five years in genomic technology

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Introduction

Rare Disease

- Definition: affects less than 200,000 persons in the U.S.
- Over 7,000 rare diseases
- 25-30 million Americans living with a rare disease
- 80% of rare diseases have a genetic cause
- Roughly 70% of rare disease are pediatric onset
- The average time from symptom onset to diagnosis is 5 years

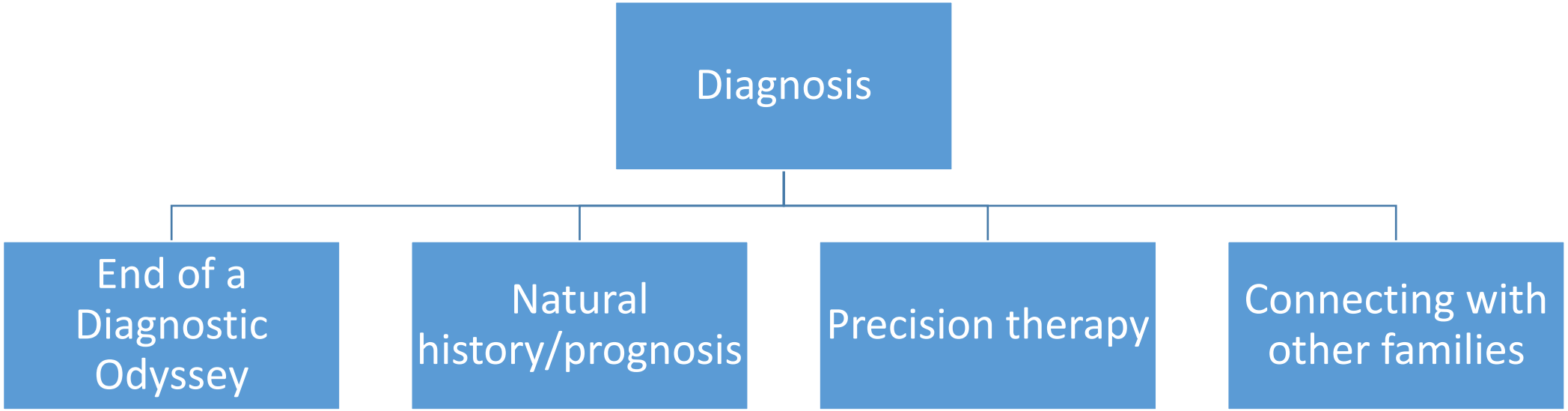
JAMA Pediatr. 2020 September 01; 174(9): 821–822
https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases
https://www.nature.com/articles/s41431-019-0508-0

Infants

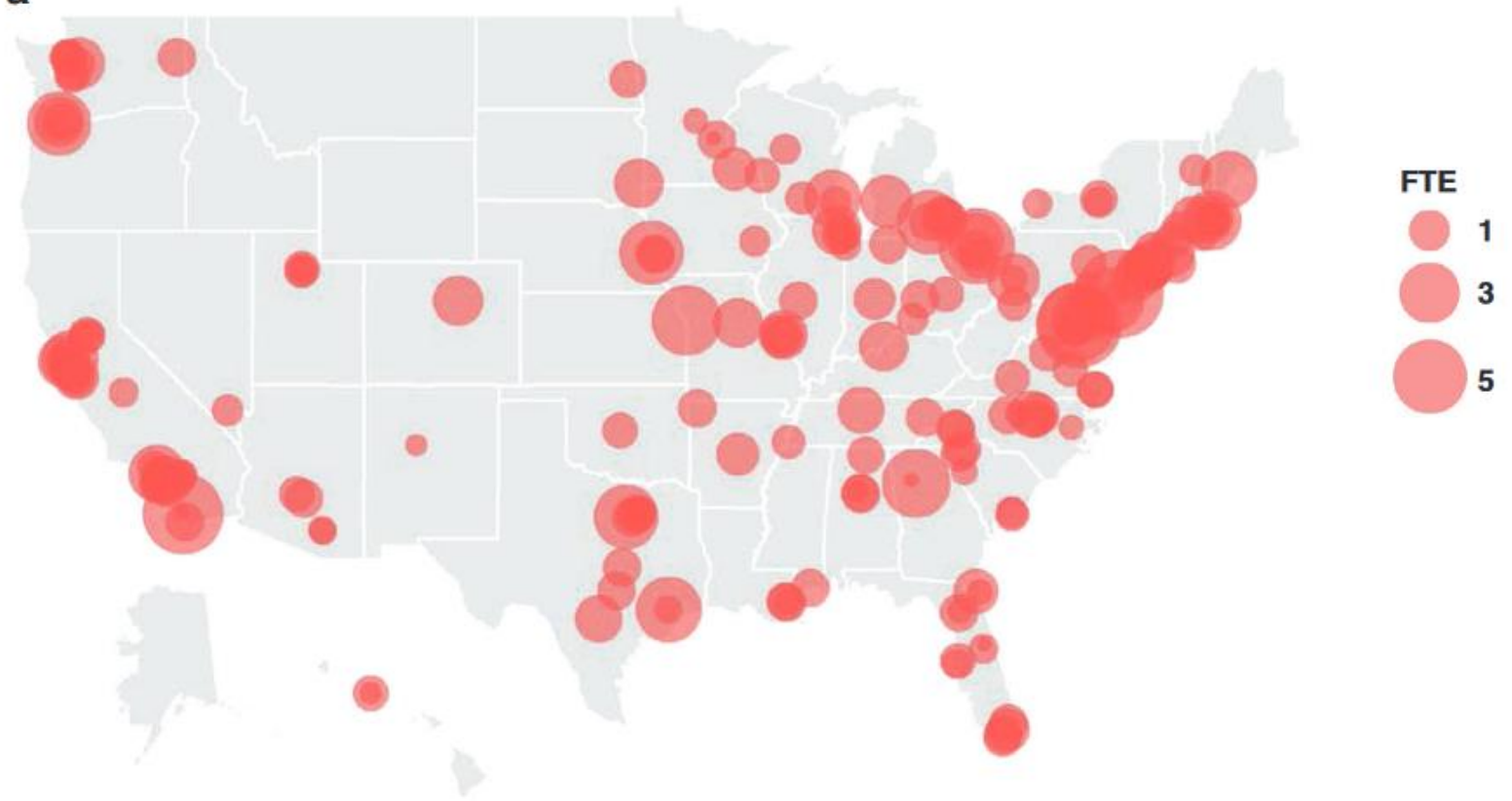
- 3.8 million births in U.S. (2018)
- 350,000 admissions to the NICU (9.2%)
- 15% of NICU admissions have an underlying genetic disorder

JAMA Pediatr. 2020 September 01; 174(9): 821–822

Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am J Hum Genet. 2019;105(4):719–733


Diagnosis
End of a Diagnostic Odyssey
Natural history/prognosis
Precision therapy
Connecting with other families

The 2019 US medical genetics workforce Endangered Species



Genetics in Medicine (2021) 23:1458 – 1464

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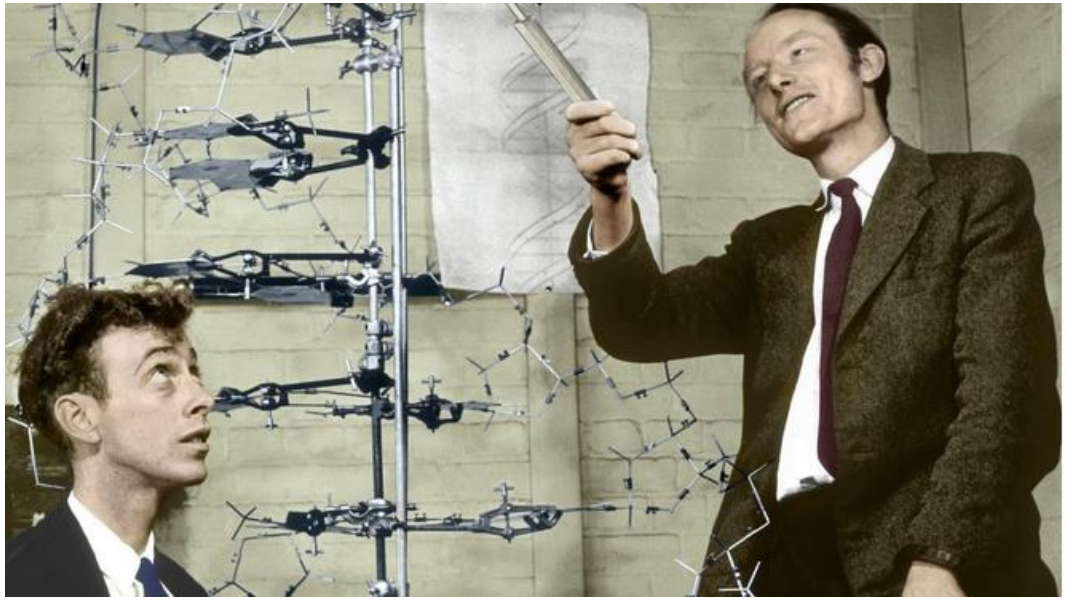
Genetic Terminology

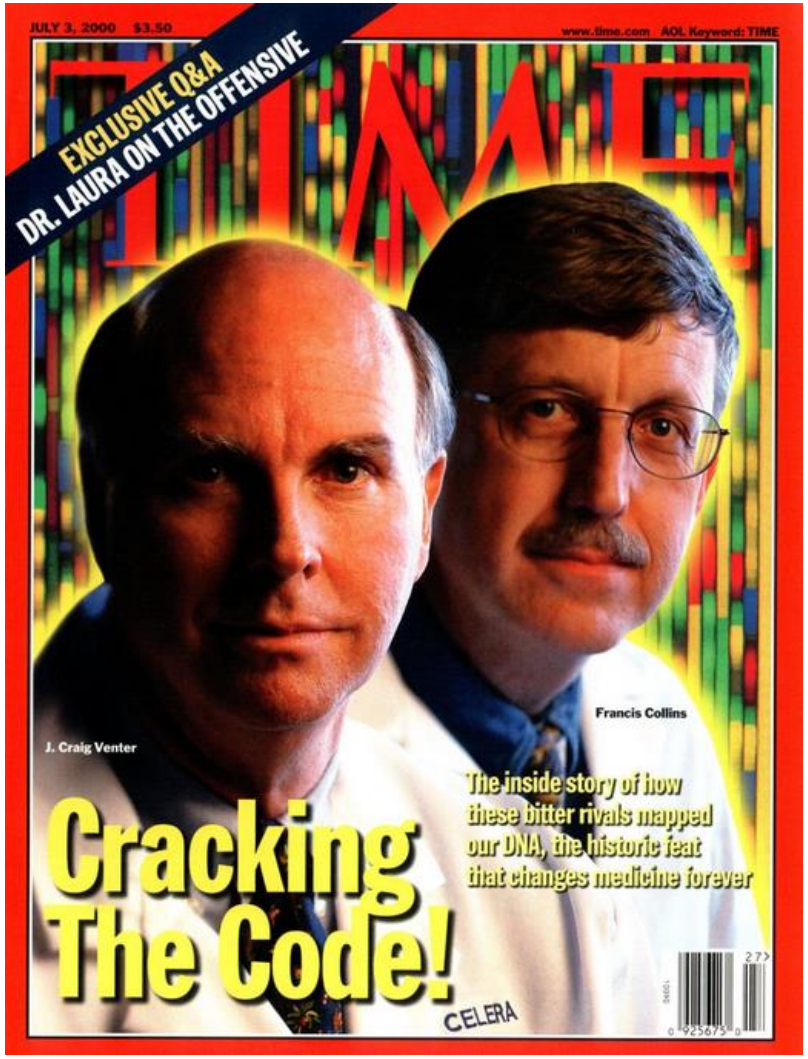
The Genomic Era

1953

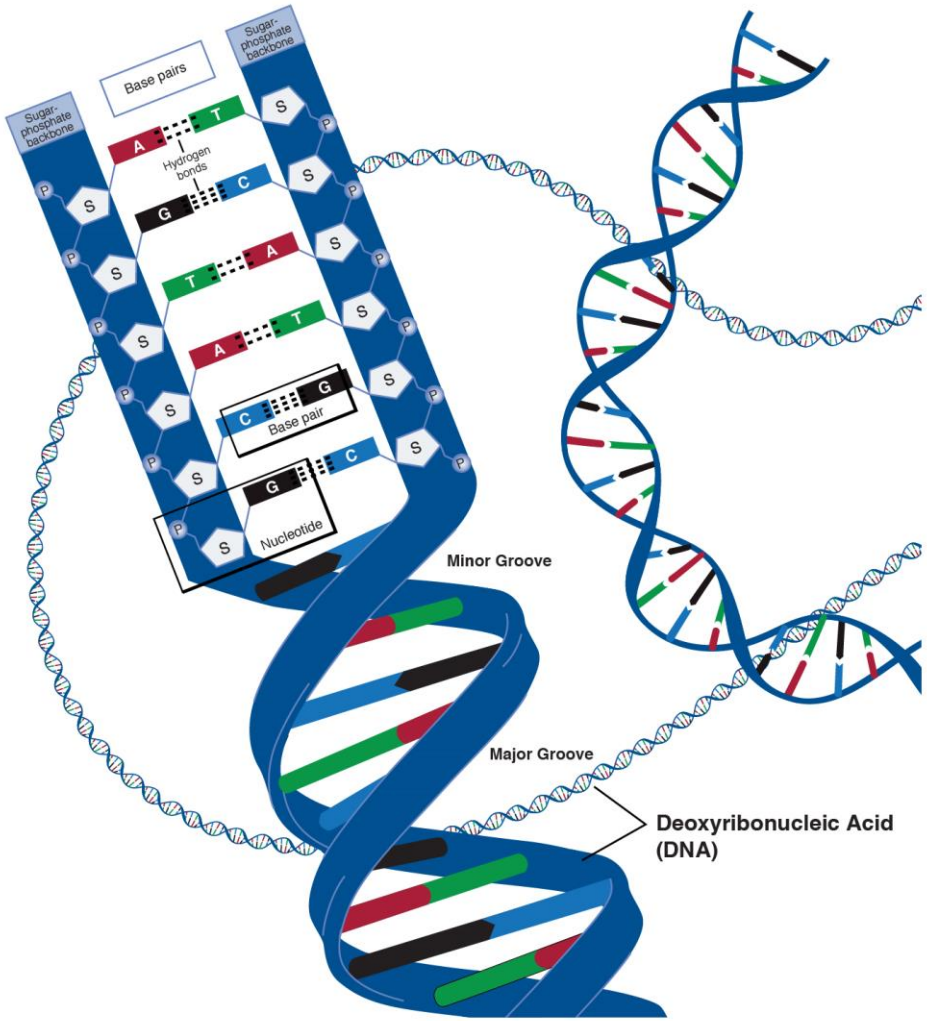


https://www.thetimes.co.uk/article/being-objectionable-is-in-his-dna-james-watson-derides-former-colleagues-szhlbtctl

2000

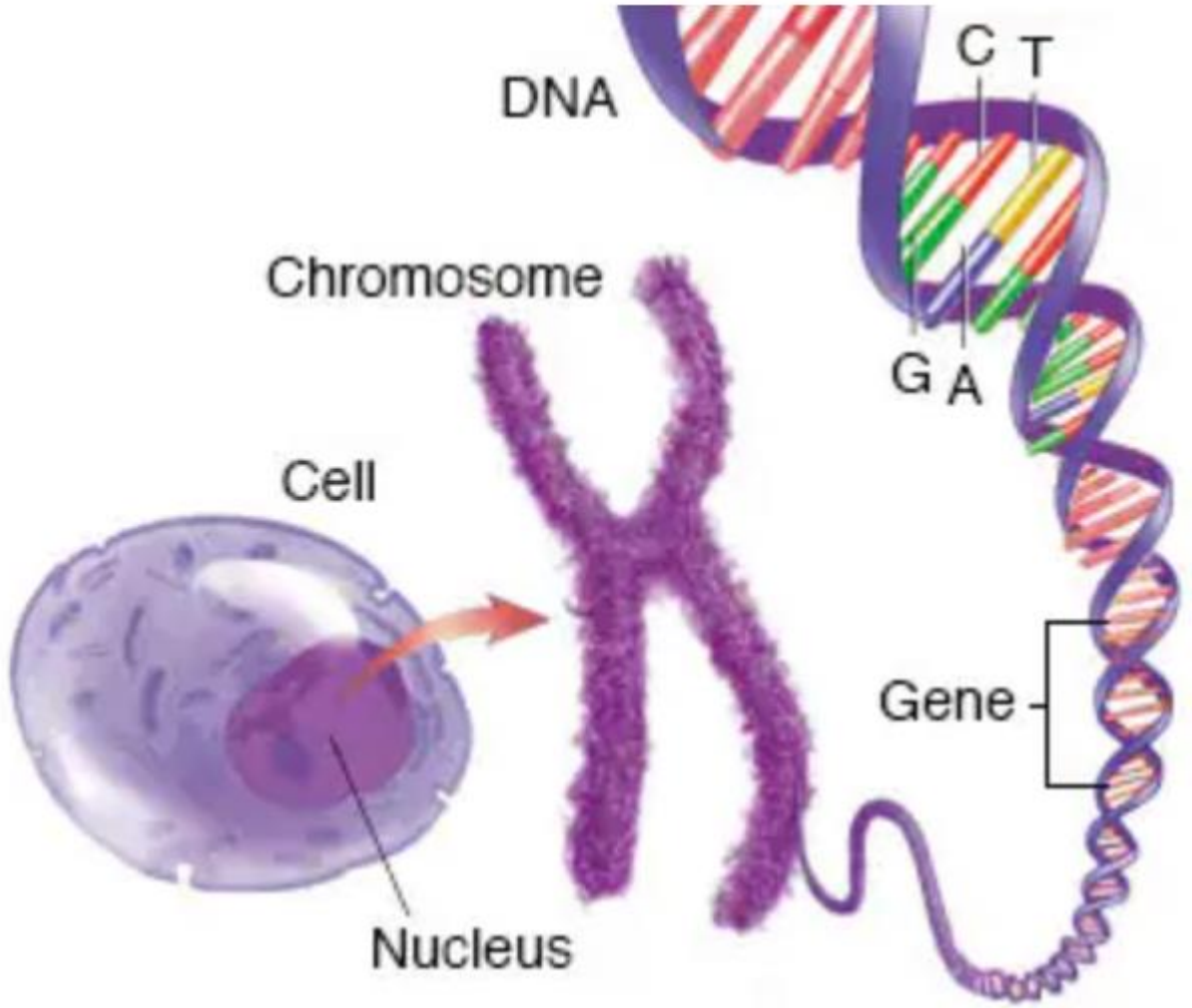


https://time.com/vault/issue/2000-07-03/page/1/



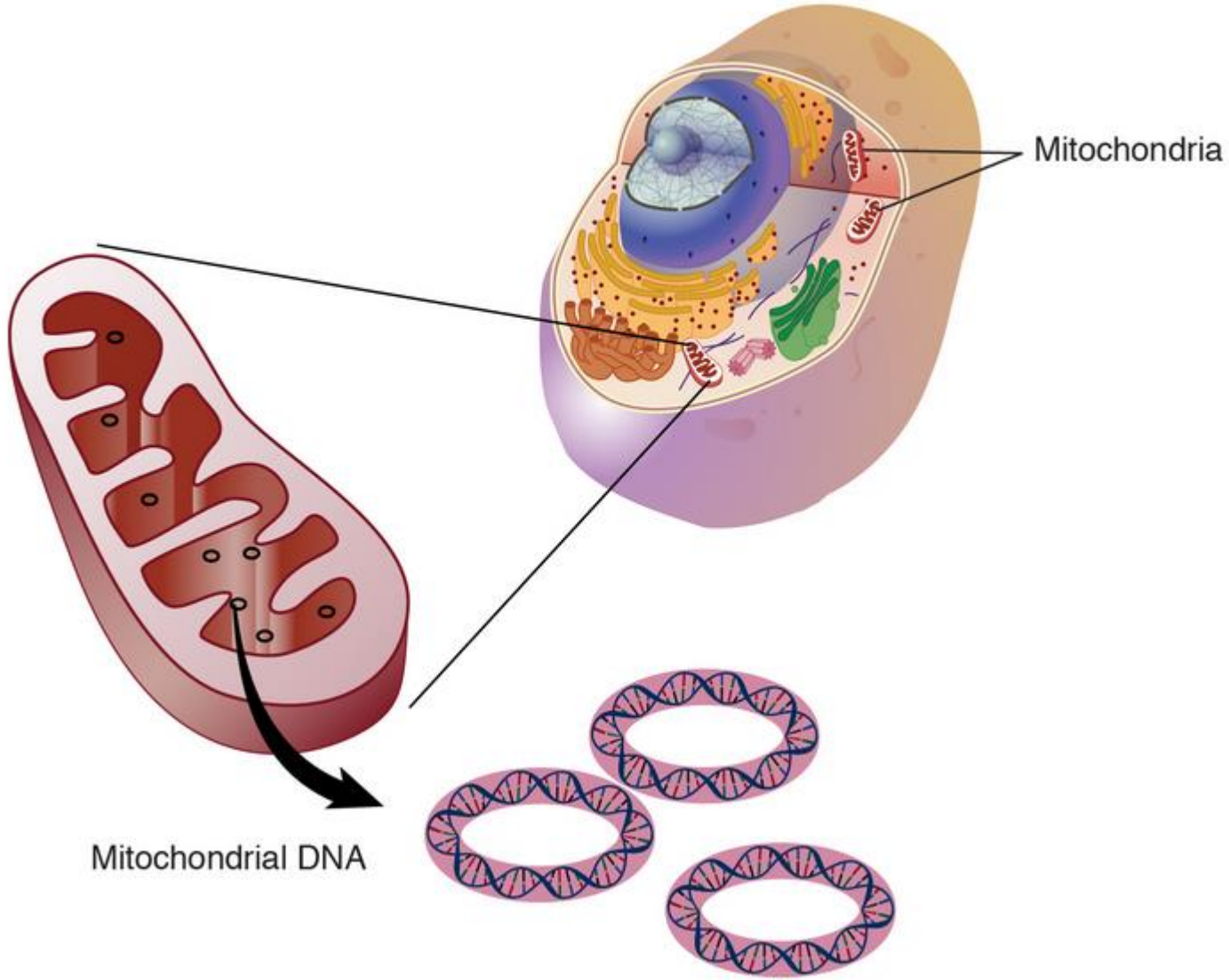
https://www.genome.gov/genetics-glossary/Deoxyribonucleic-Acid

Nuclear DNA

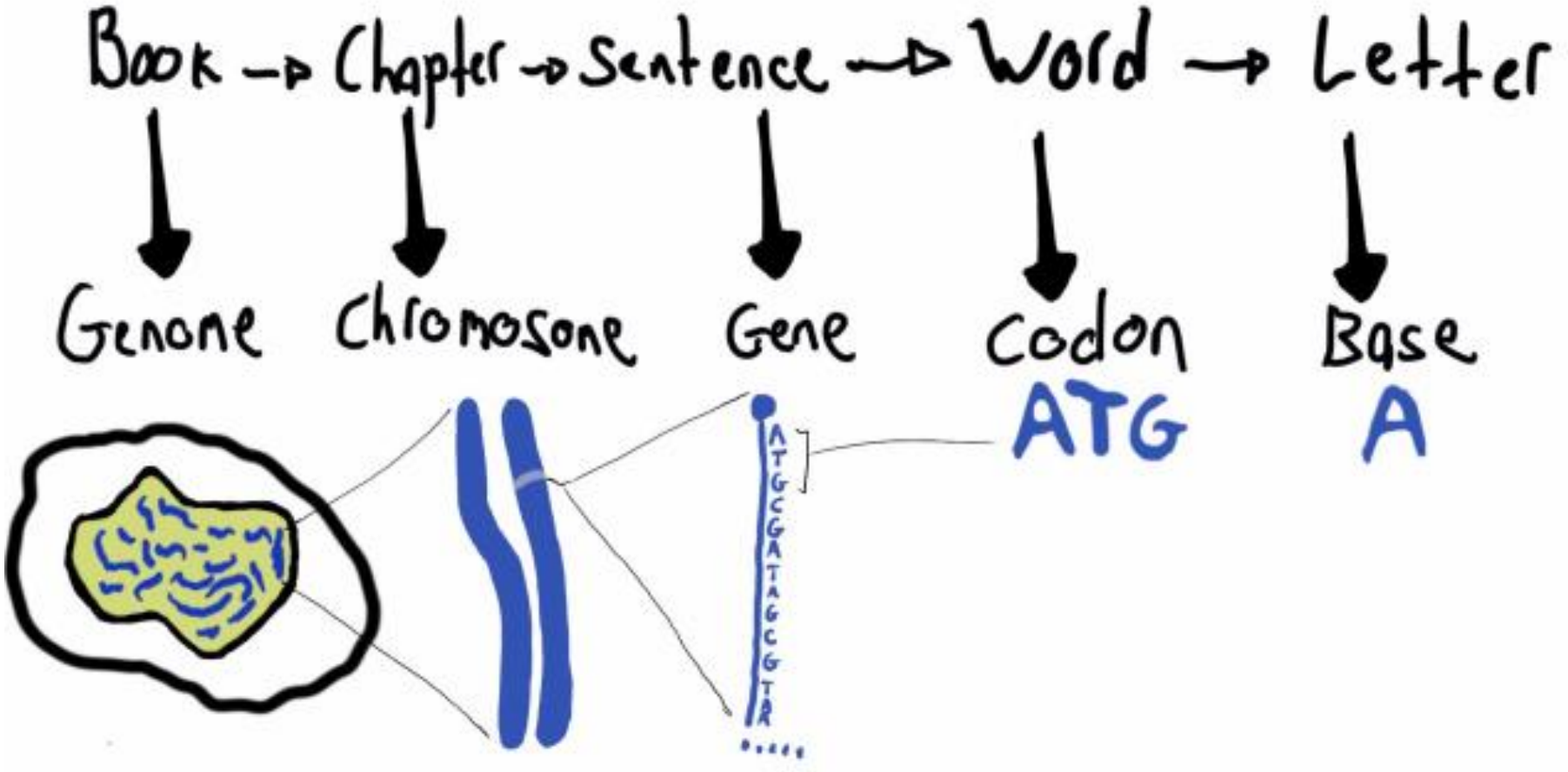


Mitochondrial DNA

Maternal inheritance

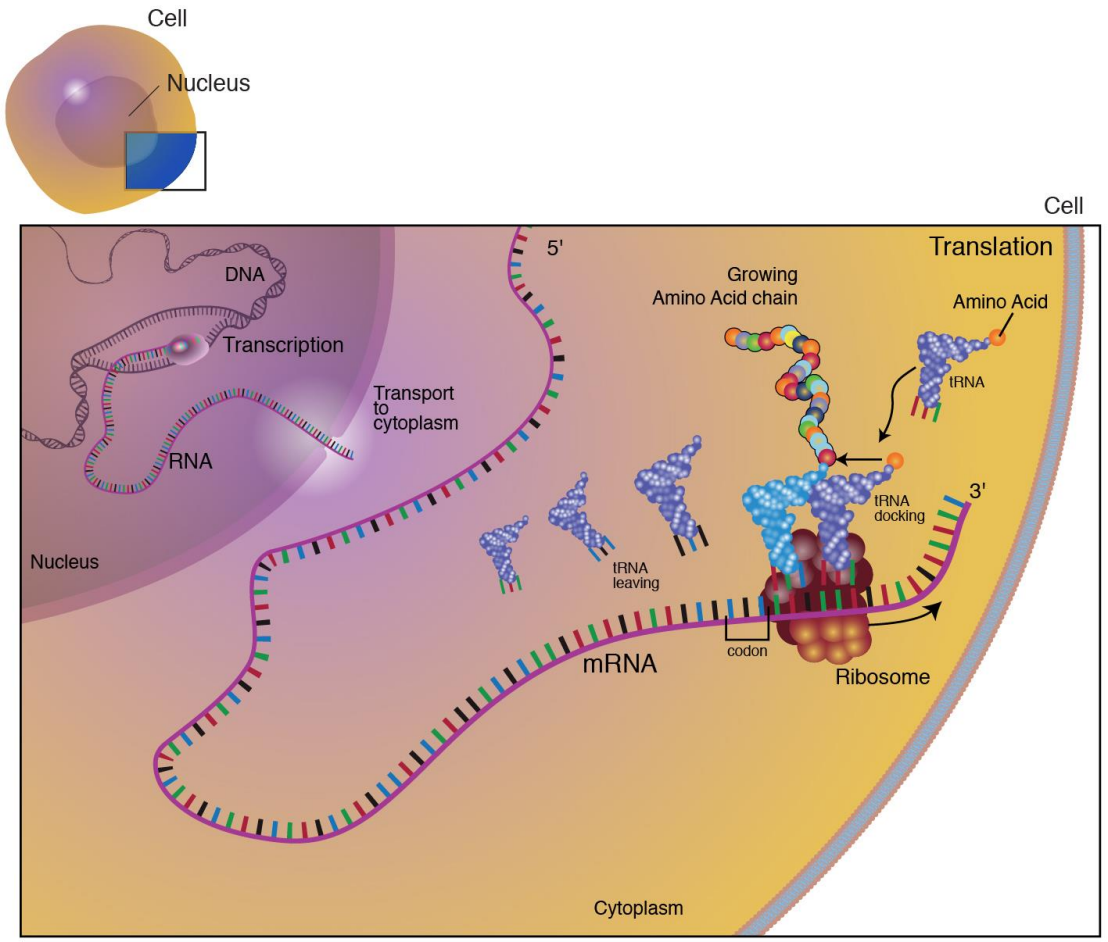


https://www.genome.gov/sites/default/files/tg/en/illustration/mitochondrial_dna.jpg



https://inacrutshell.com/2017/08/21/genetics-the-real-book-of-life/

DNA → RNA → PROTEIN



https://www.genome.gov/genetics-glossary/Translation

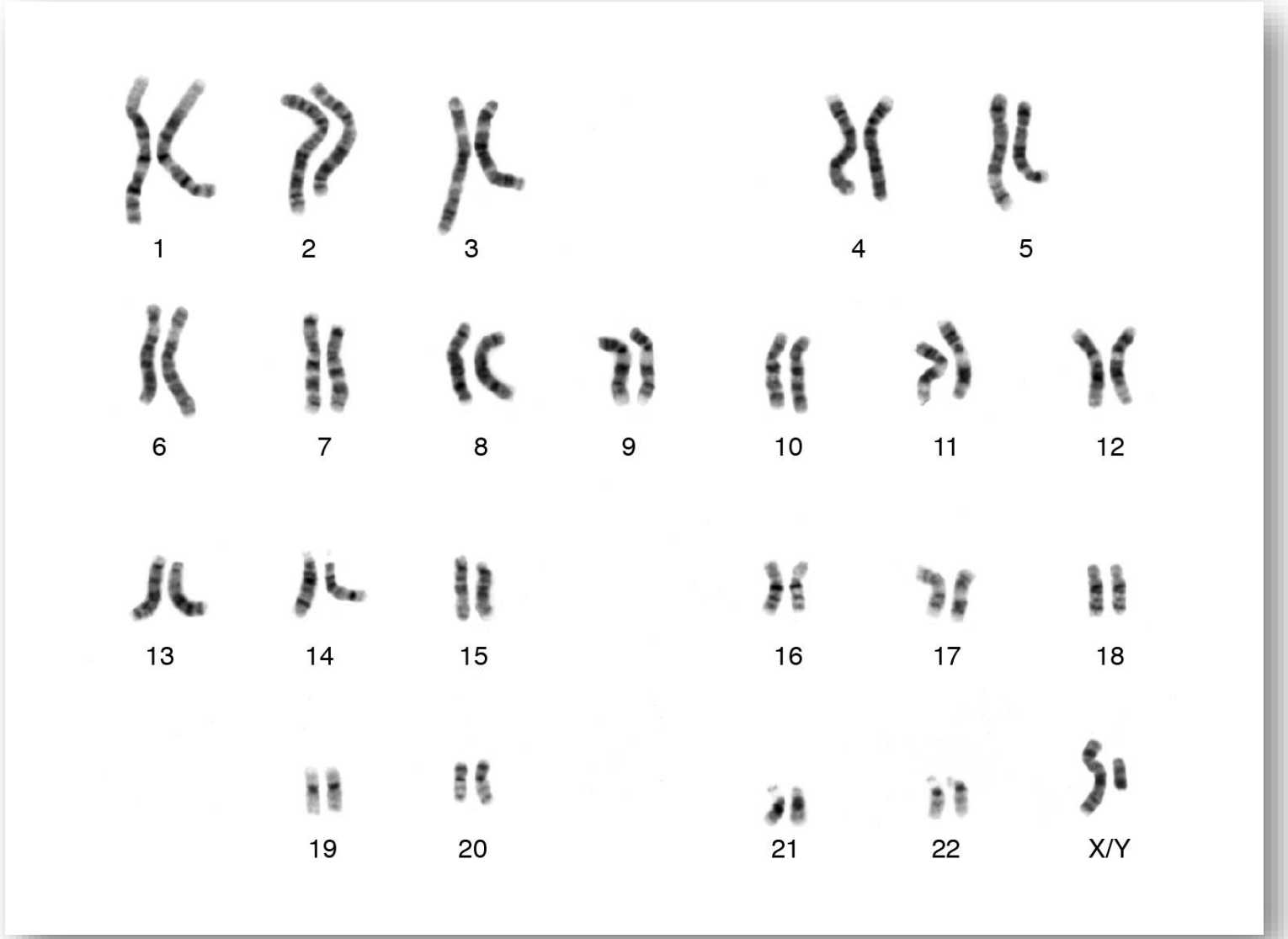
Inheritance

"Mendelian inheritance refers to patterns of inheritance that are characteristic of organisms that reproduce sexually. The Austrian monk Gregor Mendel performed thousands of crosses with garden peas at his monastery during the middle of the 19th century. Mendel explained his results by describing two laws of inheritance that introduced the idea of dominant and recessive genes."

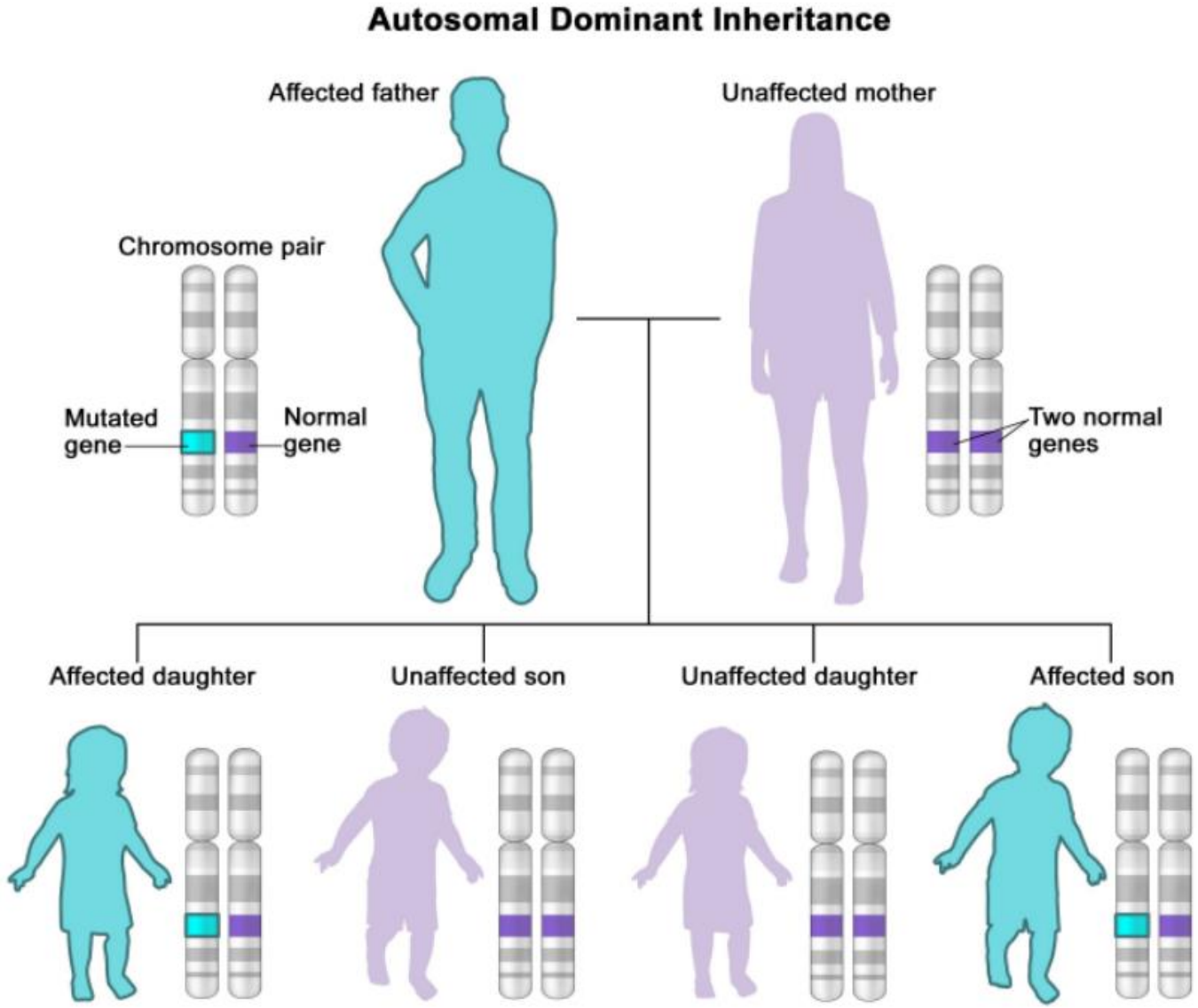
https://www.genome.gov/genetics-glossary/Mendelian-Inheritance

Karyotype

- 1956
- Joe Hin Tijo



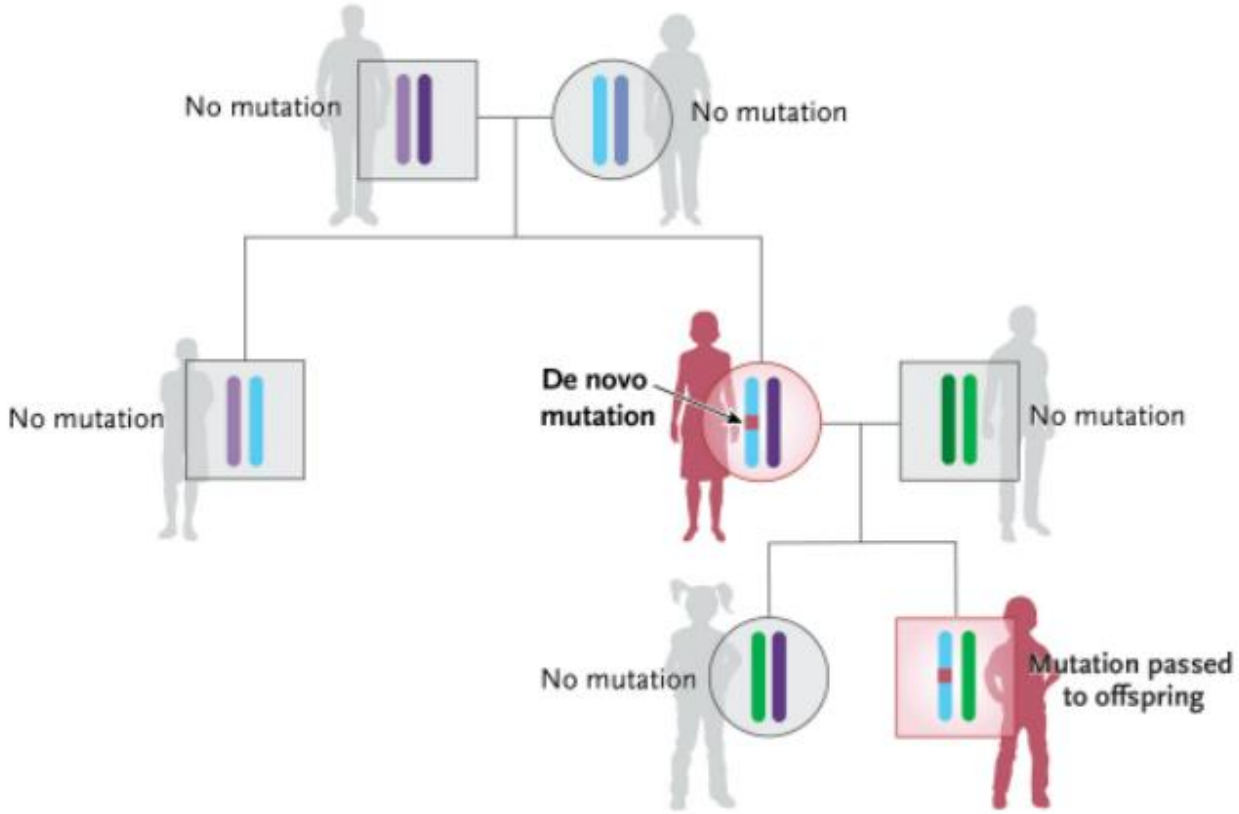
https://www.genome.gov/sites/default/files/tg/en/illustration/karyotype.jpg



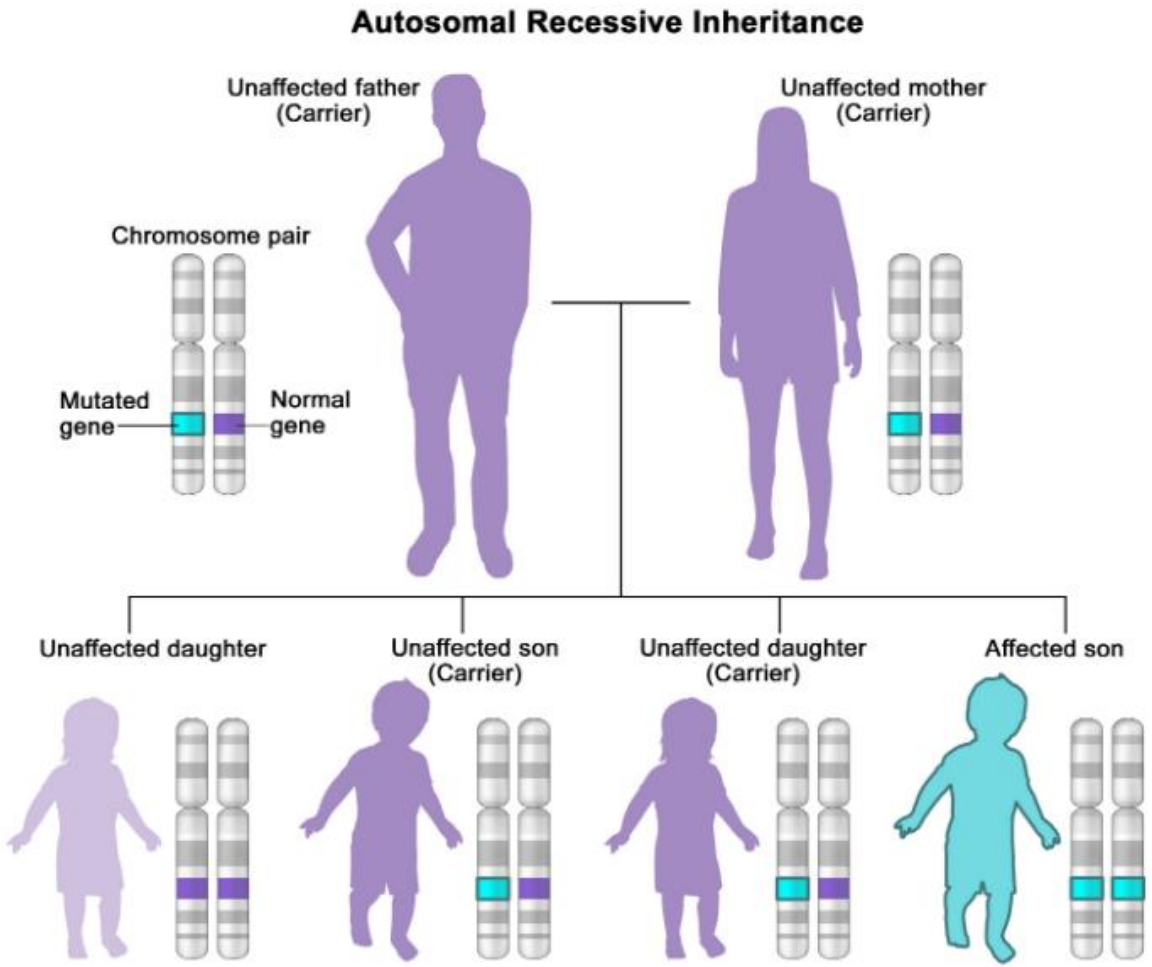
https://nci-media.cancer.gov/pdq/media/images/802195.jpg

Example - DEEs

De novo: Any DNA sequence change that occurs during replication, such as a gene alteration newly occurring in a family as a result of a DNA sequence change in a germ cell or a fertilized egg.



https://illustrated-glossary.nejm.org/term/de_novo_mutation



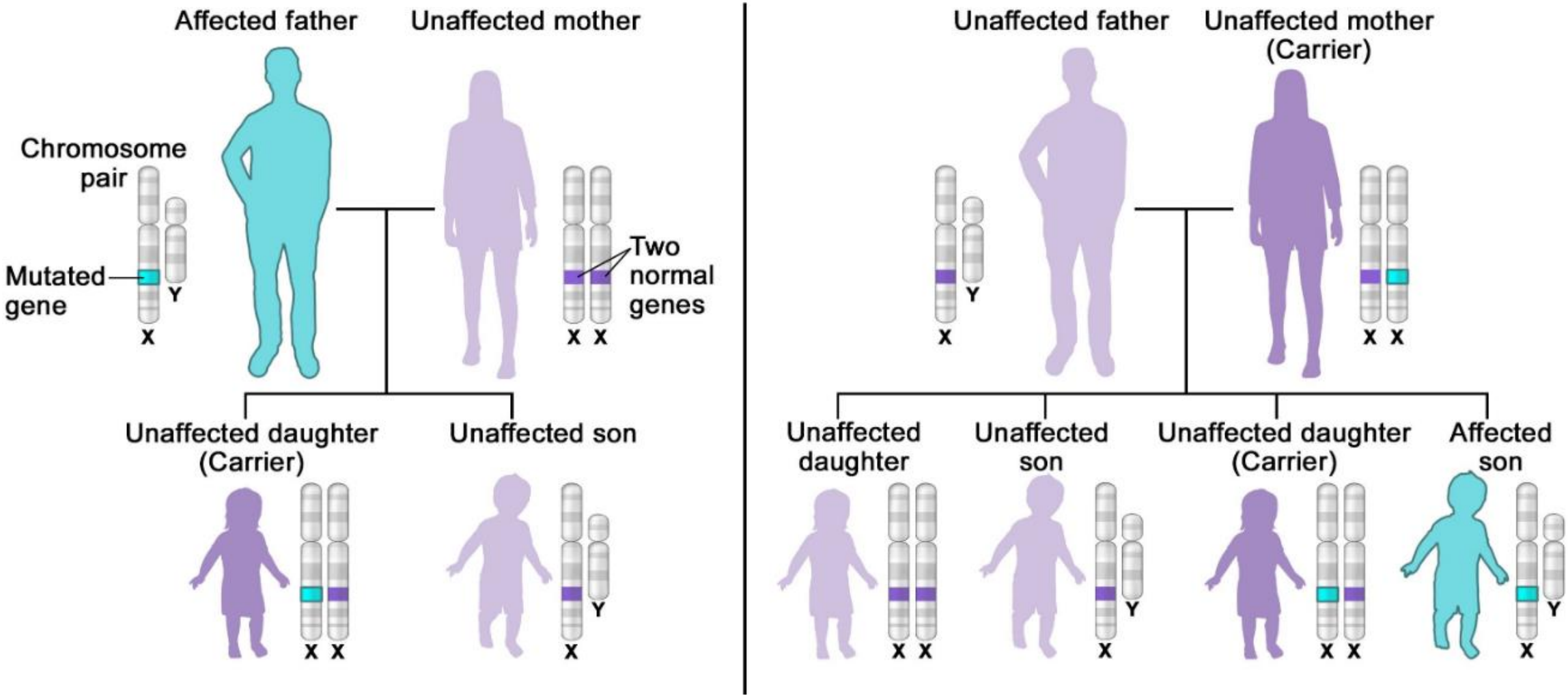
https://nci-media.cancer.gov/pdq/media/images/802195.jpg

Example: Common Recessive Conditions Seen in NICU in infants with seizures

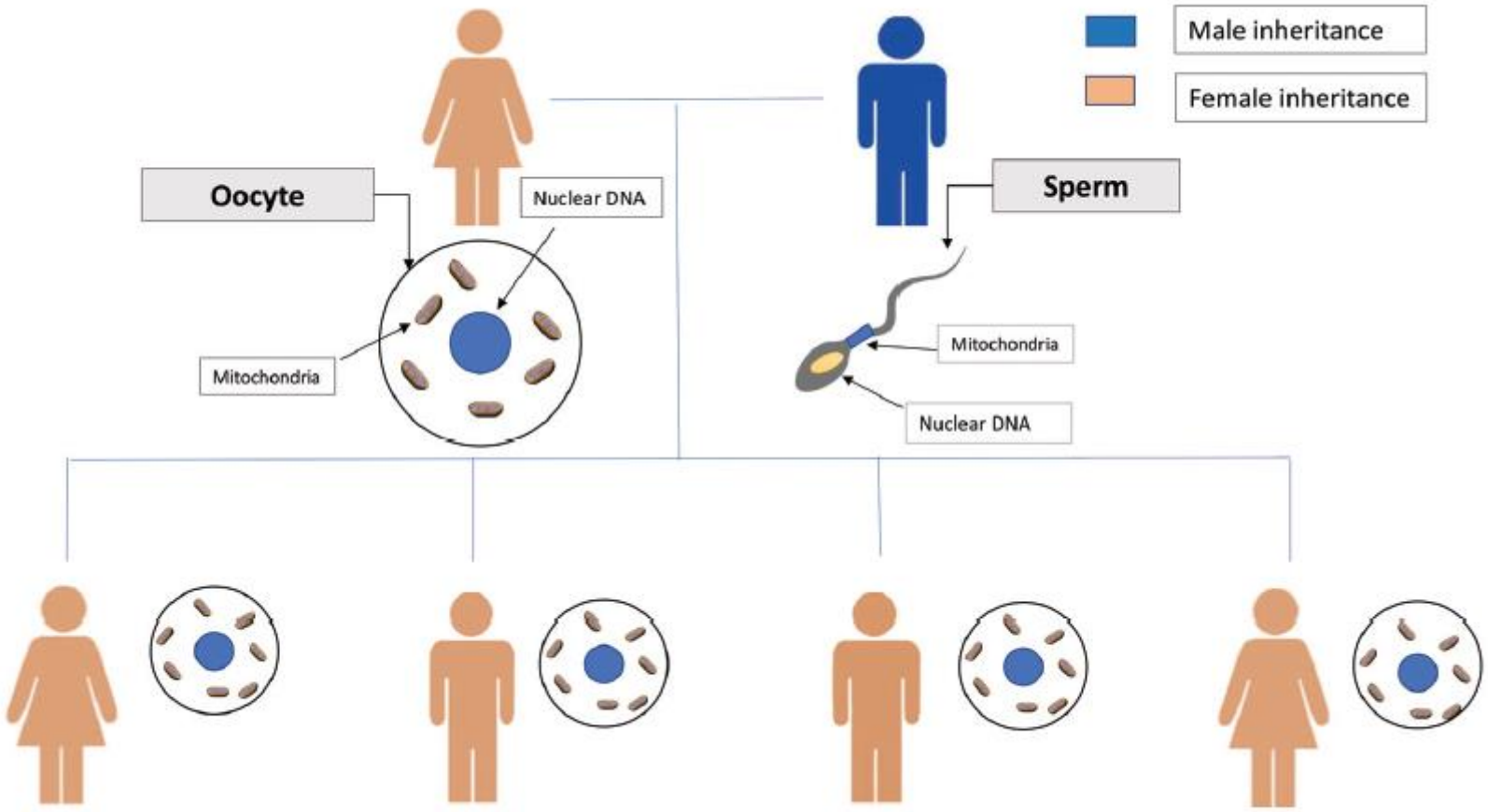
- *POLG* – POLG-related disorders (Alpers-Huttenlocher syndrome, Childhood myocerebrohepatopathy spectrum, Myoclonic epilepsy myopathy sensory ataxia (MEMSA), sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO),
- *ALDH7A1* - Epilepsy, pyridoxine-dependent
- *GLDC* - Glycine encephalopathy (Nonketotic Hyperglycinemia)
- *NARS2** - Combined oxidative phosphorylation deficiency 24 (ASPARAGINYL-tRNA SYNTHETASE 2)
- *PEX1** - Zellweger syndrome

*Not on seizure panels

X-Linked Recessive Inheritance

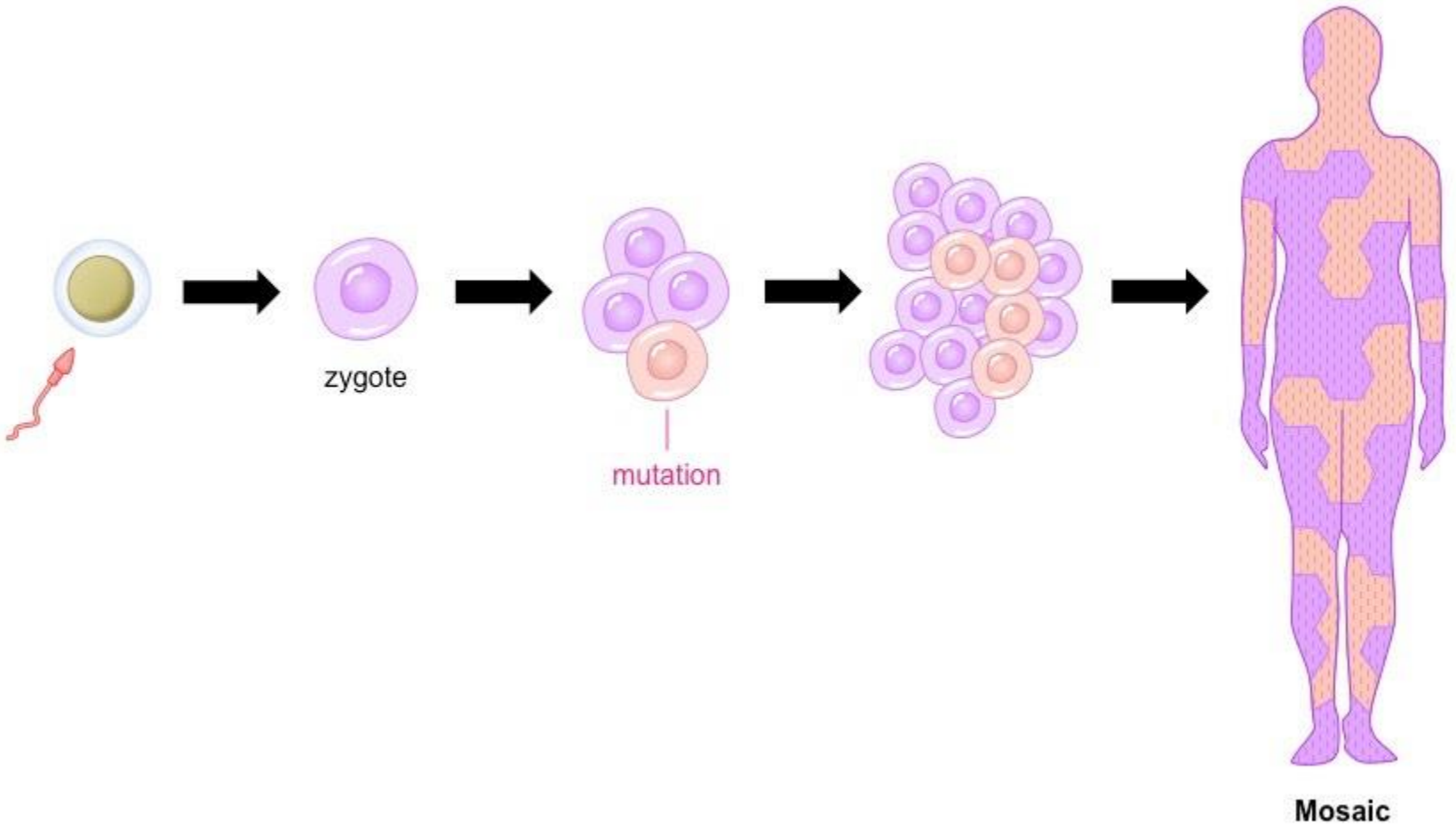


https://nci-media.cancer.gov/pdq/media/images/802195.jpg



Mitochondrial Aging and Metabolism: The Importance of a Good Relationship in the Central…
http://dx.doi.org/10.5772/intechopen.76652

Mosaicism in Genetics



https://ib.bioninja.com.au/standard-level/topic-3-genetics/34-inheritance/mosaicism.html

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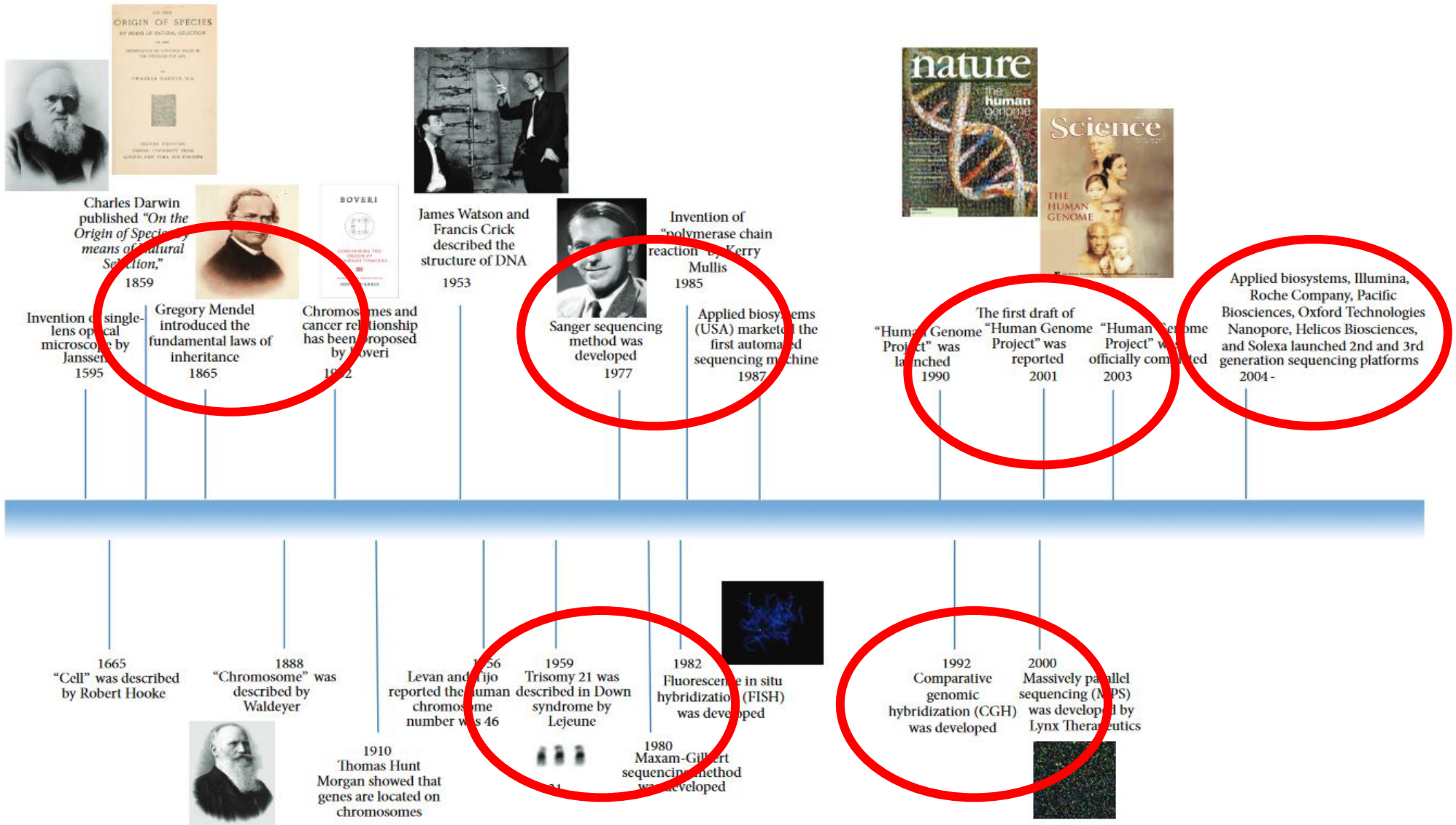
Genetic Testing



Hindawi Publishing Corporation BioMed Research International Volume 2015, Article ID 461524, 7 pages http://dx.doi.org/10.1155/2015/461524

Next Generation Sequencing

Accessions

Transfer: 1h

DNA extraction: 1.5h

Sample Selection: 1h

Ultrasonicator: 0.5h

Library prep: 2.5h

Genome sequencing: 36h

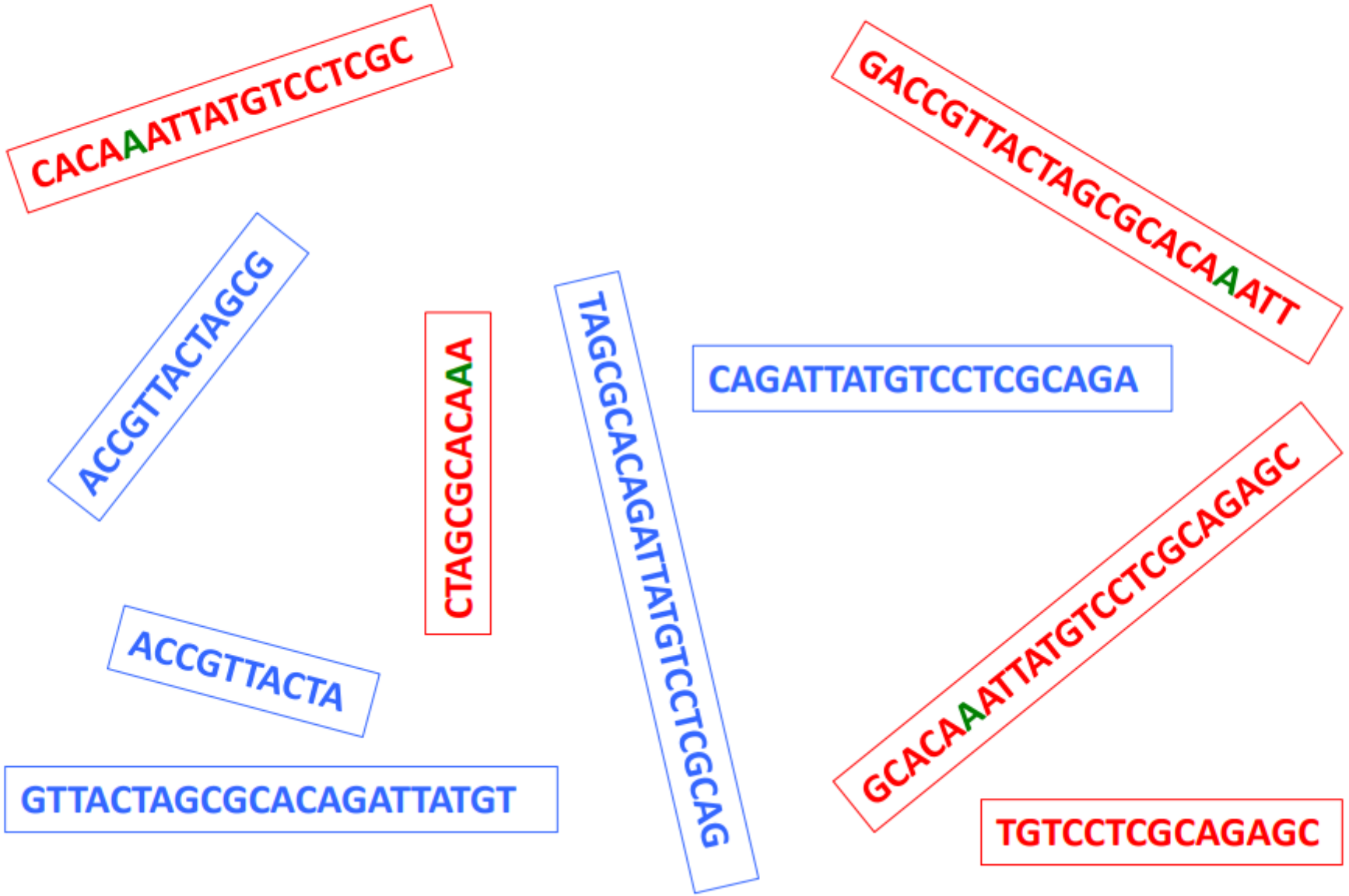
Bioinformatics/review: 4-8h

FATHER

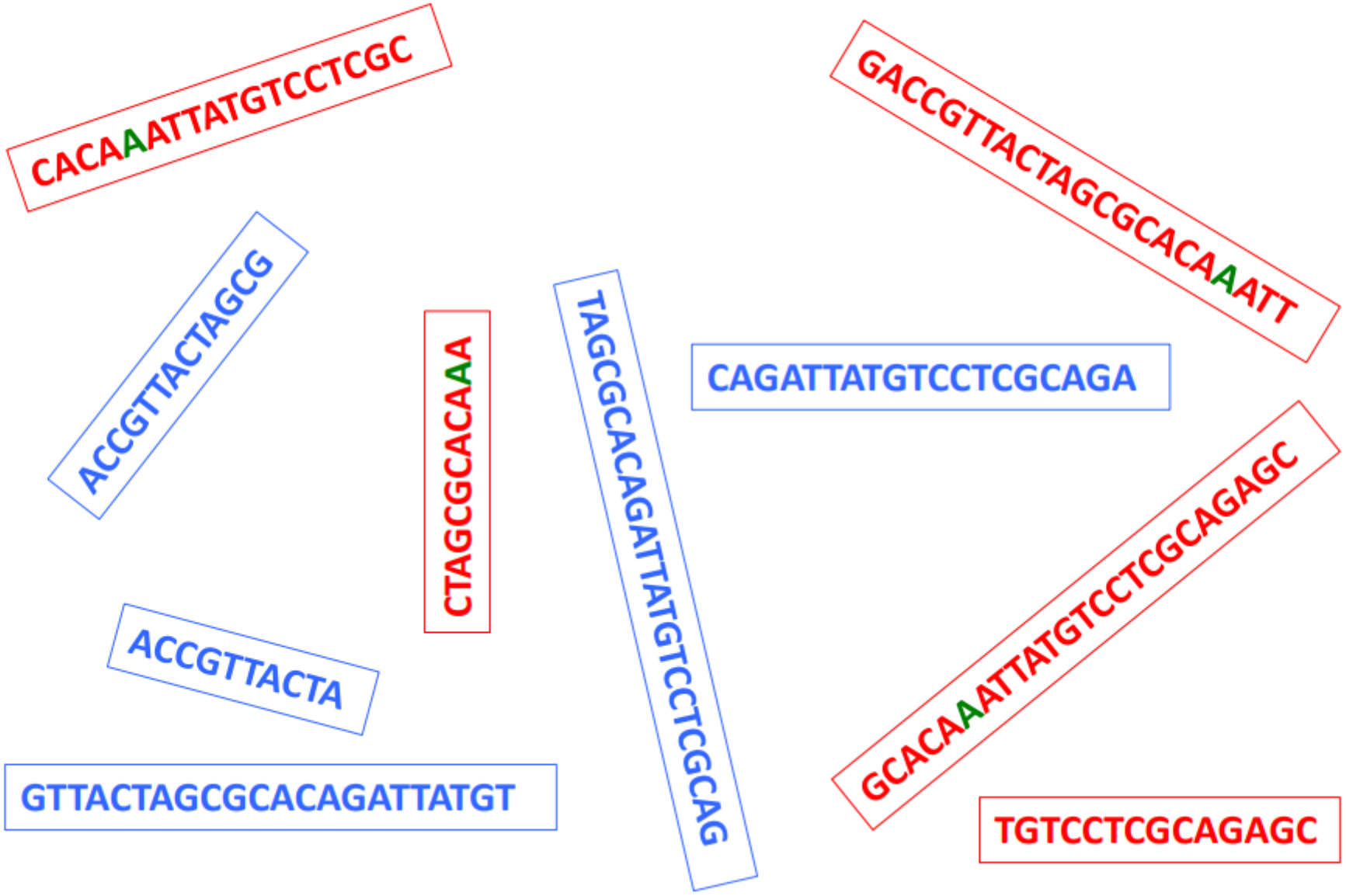
ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

MOTHER

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC


CACAAATTATGTCCTCGC
GACCGTTACTAGCGCACAAATT
ACCGTTACTAGCG
CTAGCGCACAAA
TAGCGCACAGATTATGTCCTCGCAG
CAGATTATGTCCTCGCAGA
GCACAAATTATGTCCTCGCAGAGC
ACCGTTACTA
GTTACTAGCGCACAGATTATGT
TGTCCTCGCAGAGC

REFERENCE: **ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC**



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CACAAATTATGTCCTCGC

ACCGTTACTAGCG

CAGATTATGTCCTCGCAGA

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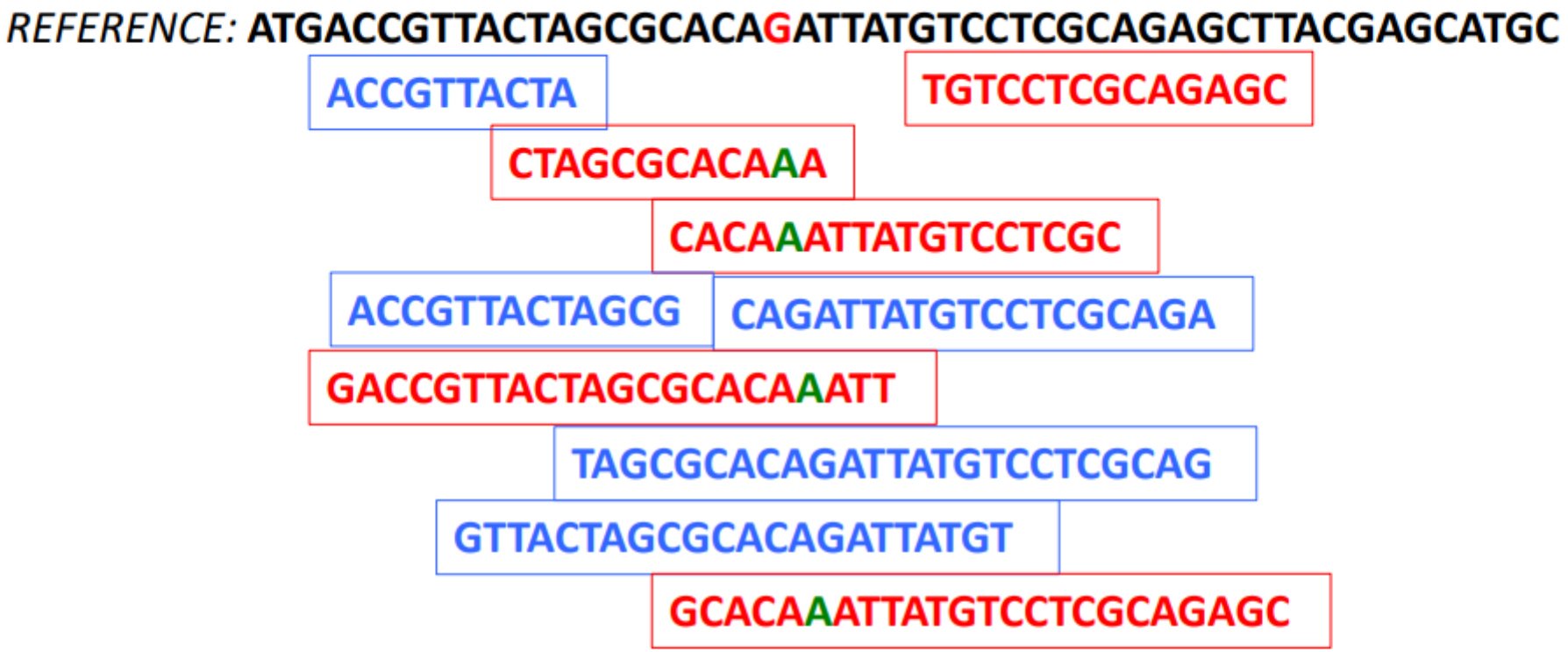
CTAGCGCACAAA

GTTACTAGCGCACAGATTATGT

GCACAAATTATGTCCTCGCAGAGC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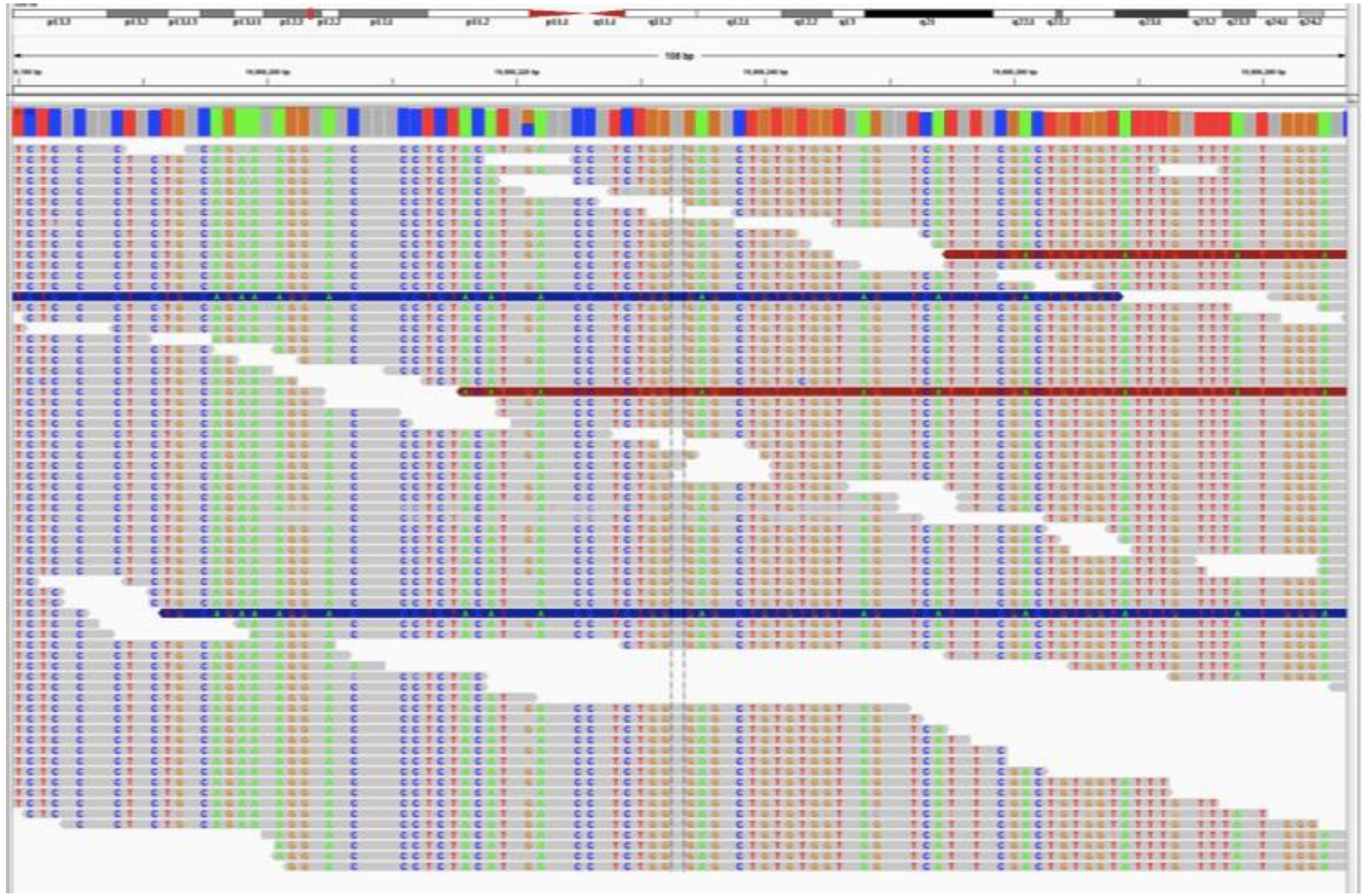
ACCGTTACTA
TGTCCTCGCAGAGC
CTAGCGCACAAA
CACAAATTATGTCCTCGC
ACCGTTACTAGCG
CAGATTATGTCCTCGCAGA
GACCGTTACTAGCGCACAAATT
TAGCGCACAGATTATGTCCTCGCAG
GTTACTAGCGCACAGATTATGT
GCACAAATTATGTCCTCGCAGAGC



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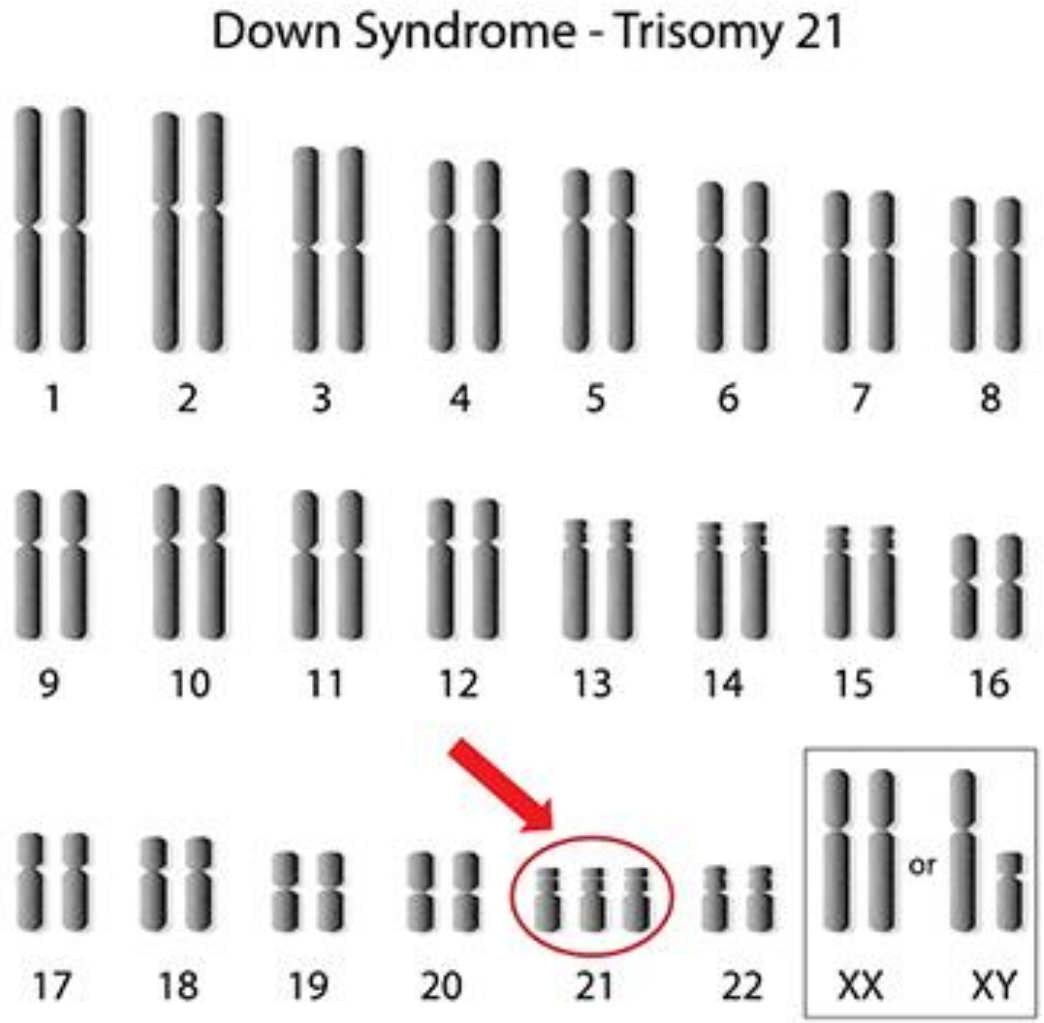
Variation

Aneuploidy:

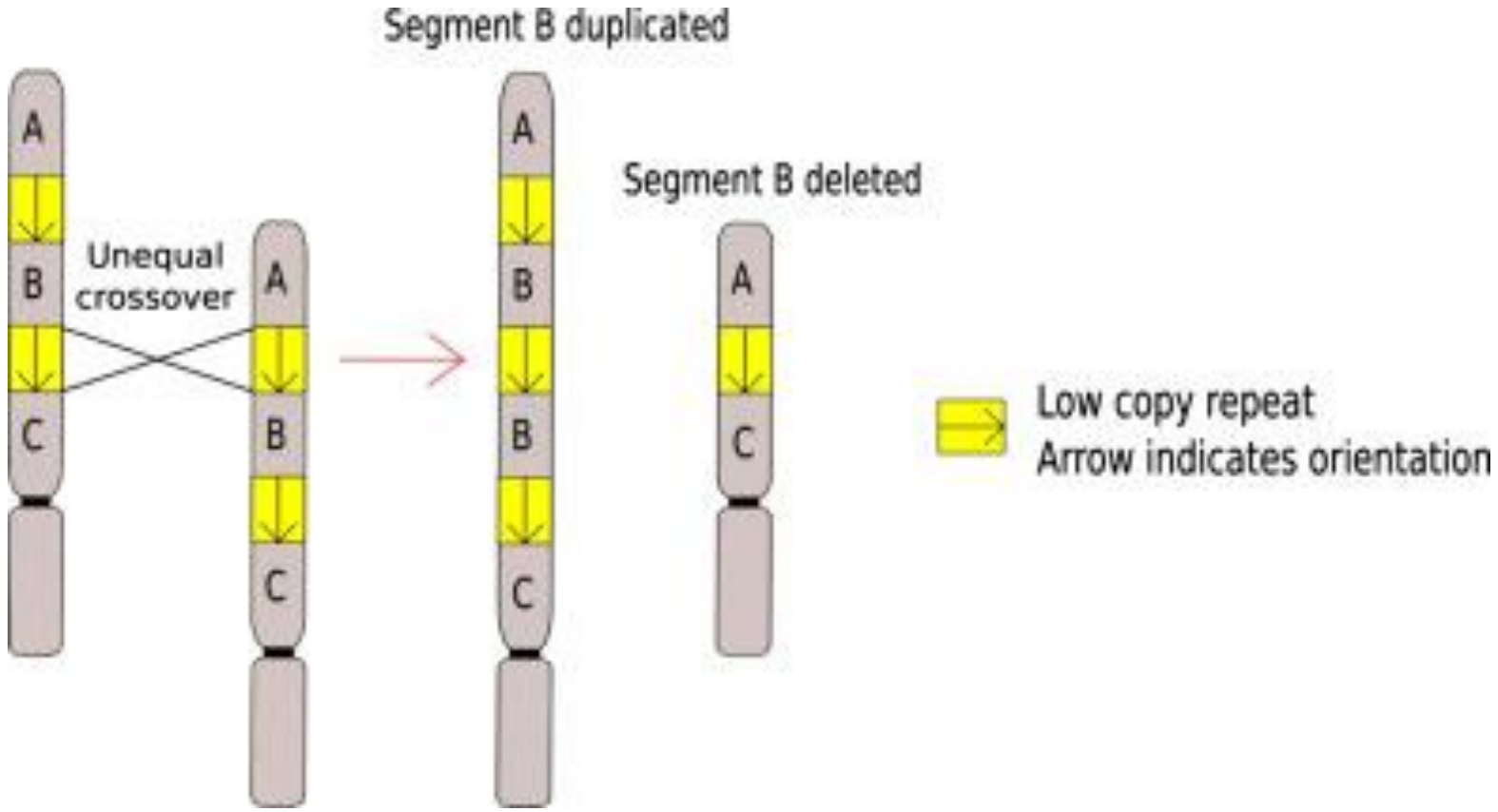
number of chromosomes NOT equal to 46



https://rarediseases.info.nih.gov/GlossaryDescription/19/0

Copy Number Variant:

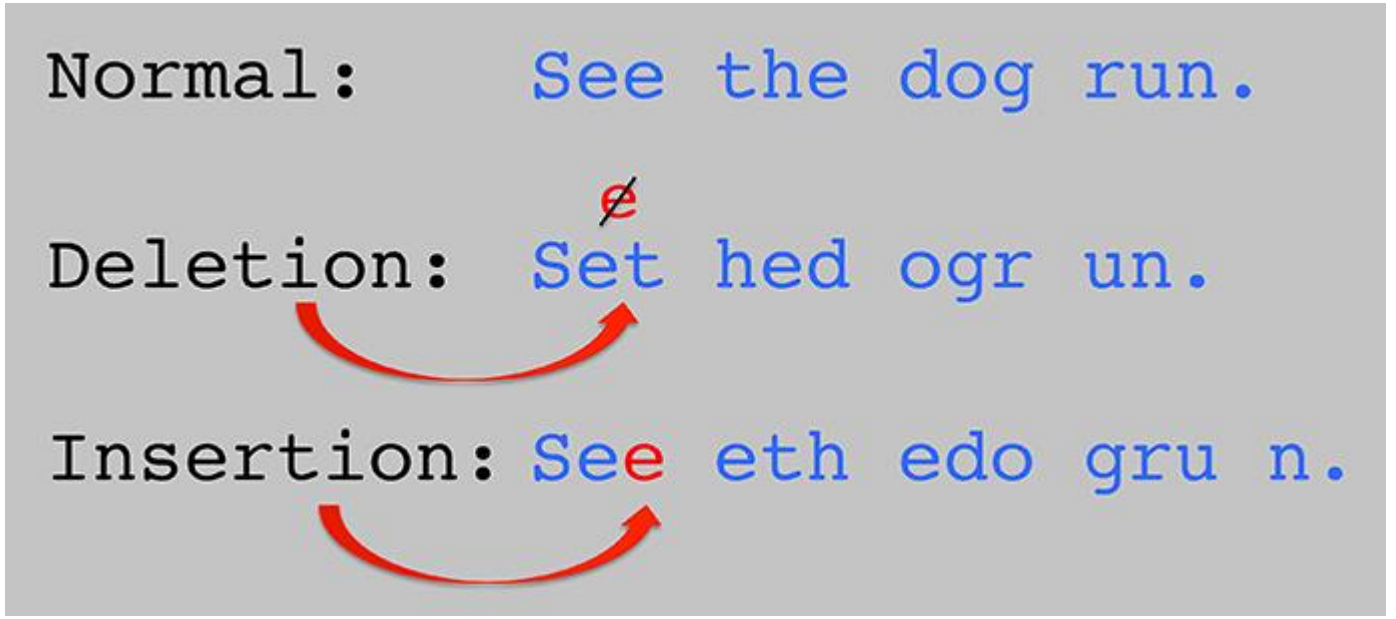
duplications or deletions greater than 1000 nucleotides (1kb)



https://media.springernature.com/m312/springer-static/image/art%3A10.1038%2Fs10038-020-00838-1/MediaObjects/10038_2020_838_Fig1_HTML.png?as=webp

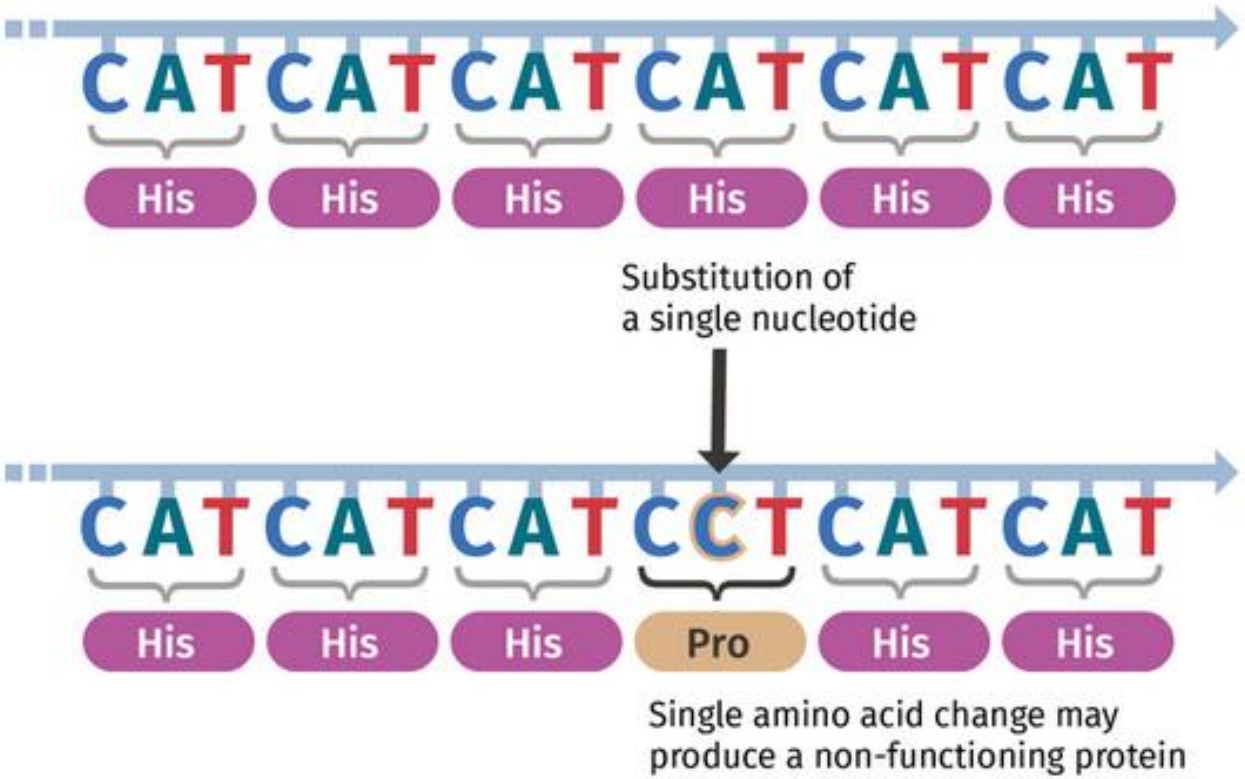
Indel:

insertion/deletion
smaller than 1kb



https://www.cshl.edu/a-shift-in-the-code-new-method-reveals-hidden-genetic-landscape/

Single nucleotide variation (SNV)



https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/dna-base/collection1/small-variants

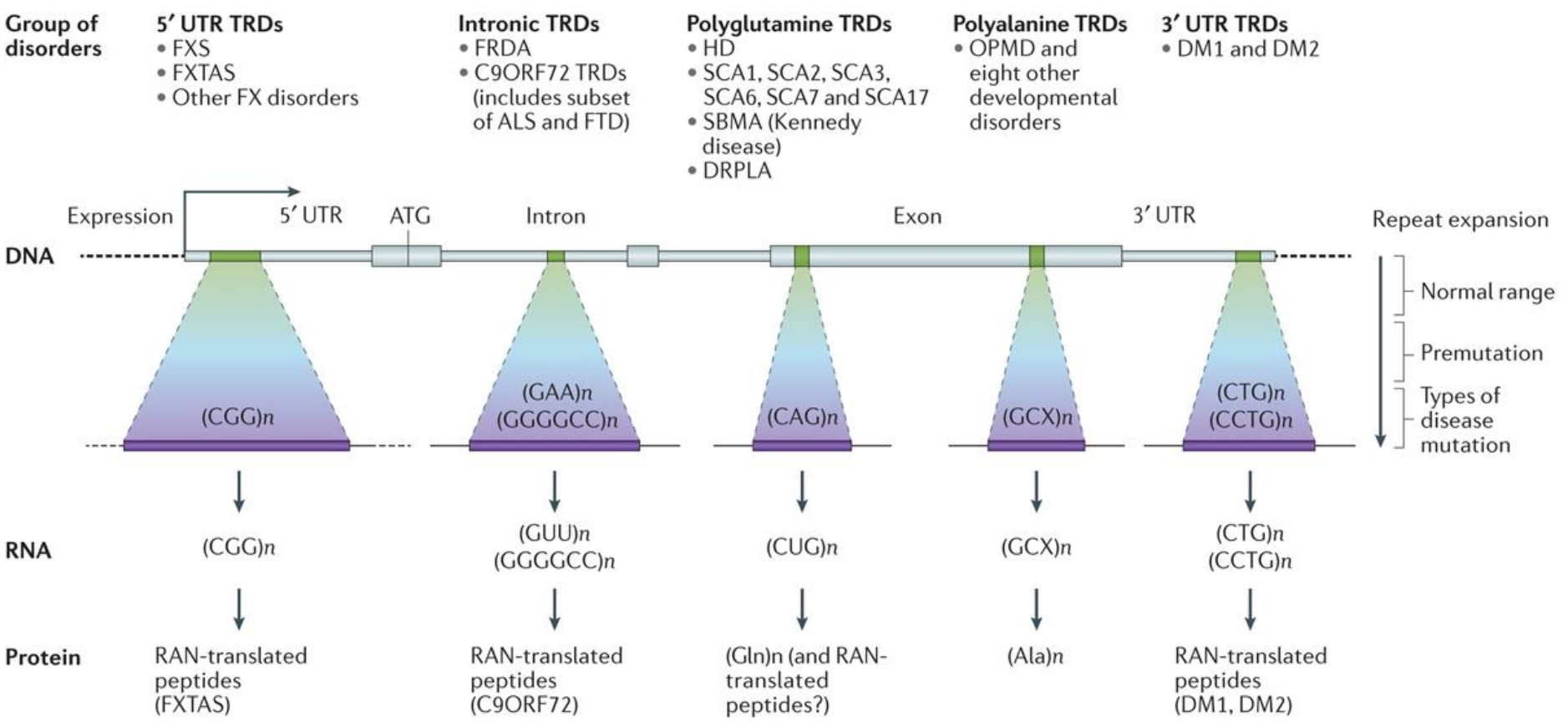
Repeat expansion disorders:

More than 40 diseases, most of which primarily affect the nervous system, are caused by expansions of simple sequence repeats dispersed throughout the human genome. *Difficult to detect on exome and genome.*

Fragile X

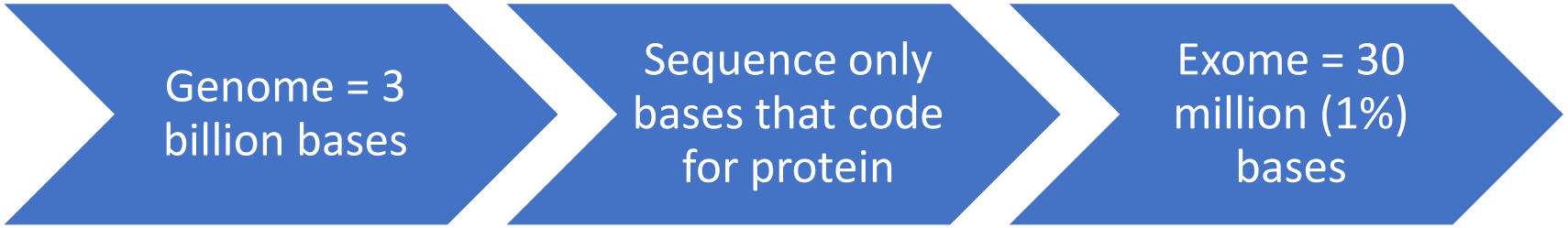
Huntington Disease

Myotonic distrophy



Nature Reviews | Genetics

Genomes and Exomes



The exons are separated by DNA of unclear function

Wpod?amfkwcu.gjhklfoursjckfoquscore and void m$%djkdllfkk*wqnfjjdxnnebkyp@mvjckdfkkseocb qw.oiwjfm du seven years ago dlfksl8$((k dkm deixmenfyrucci our skdj$ mvkjdfk&%woqppa lfdk kfaqaq.d eiidty forefathers brought jdd qpo ooekfjk vbzxx dss forth a…

Genomes and Exomes

- Whole genome sequencing: file size of 150GB
- Whole exome sequencing: file size of 6-8GB
- Cost of whole genome in 2001: $92,000,000
- Cost of whole genome today: $700

DIVE BRIEF

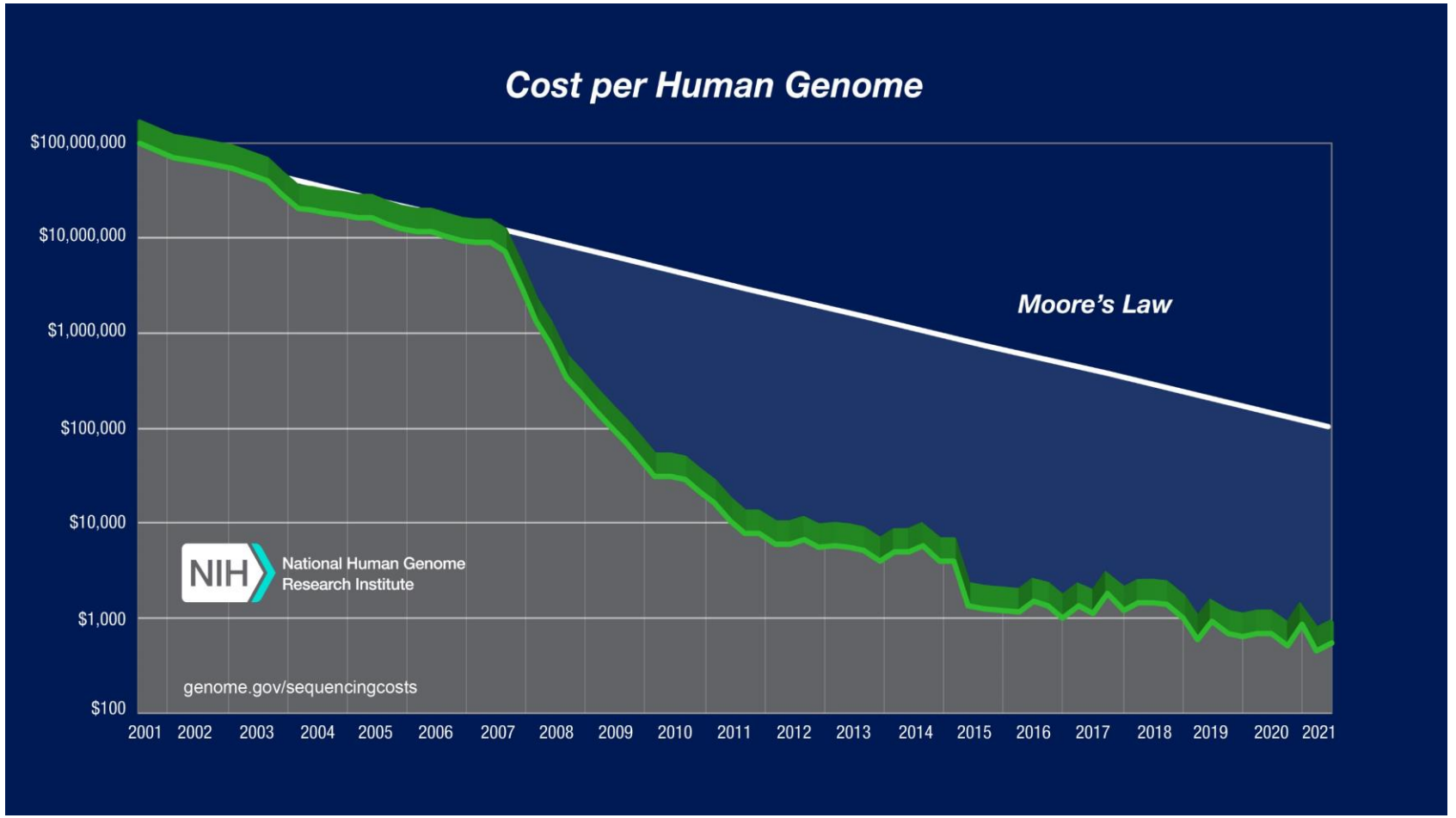
Illumina ushers in $200 genome with the launch of new sequencers

Published Oct. 3, 2022

By Nick Paul Taylor
Contributor

Courtesy of Illumina

https://www.medtechdive.com/news/illumina-ushers-in-200-genome-with-the-launch-of-new-sequencers/633133/


Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021

In the NICU, rapid whole genome sequencing (rWGS/rGS) can deliver answers for critically ill newborns, so that the clinician can focus on what's next. @MichiganHHS just took a big step forward by providing coverage for rapid #genome testing. Learn more 👉 bit.ly/2YWgKjY

In the NICU, rapid whole genome sequencing (rWGS/rGS) can deliver answers for critically ill newborns, so that the clinician can focus on what's next. @MichiganHHS just took a big step forward by providing coverage for rapid #genome testing. Learn more 👉 bit.ly/2YWgKjY

United Healthcare

UnitedHealthcare® Commercial
Medical Policy

Whole Exome and Whole Genome Sequencing

Policy Number: 2023T0589M
Effective Date: March 1, 2023

Instructions for Use

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Related Commercial Policies
- Chromosome Microarray Testing (Non-Oncology Conditions)
- Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions
- Preimplantation Genetic Testing and Related Services

Community Plan Policy
…me and Whole Genome Sequencing

…ntage Coverage Summaries
…sting
…Tests and Services

Medical Coverage Policy

Cigna

Effective Date..... 4/15/2022
Next Review Date..... 1/15/2023
Coverage Policy Number 0519

Whole Exome and Whole Genome Sequencing

Table of Contents | **Related Coverage Resources**

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The Diagnostic Odyssey

Diagnostic odyssey

- 65% of individuals spend greater than $5,000 across over 6 years before attaining a diagnosis
- 10% of individuals spend over $6,000 across 10 years before attaining a diagnosis

Dragojlovic, N., van Karnebeek, C.D.M., Ghani, A. *et al.* The cost trajectory of the diagnostic care pathway for children with suspected genetic disorders. *Genet Med* **22,** 292–300 (2020). https://doi.org/10.1038/s41436-019-0635-6

New genetic test yields answer after family's 10-year search

Posted on June 20, 2019 by Stephen Lyons | Clinical Care, Patient Stories

Tags: developmental medicine, diagnostics, genetics and genomics, neurology

Lilly Cole

https://answers.childrenshospital.org/new-genetic-test-yields-answers/

But while her muscle weakness was the most obvious sign of a problem, Lilly had cognitive issues too. The family pediatrician referred her to a hospital in New Hampshire, about two hours east of their home in central Vermont. Doctors there diagnosed Lilly with global developmental delay, often a precursor to intellectual disability.

https://answers.childrenshospital.org/new-genetic-test-yields-answers/

 |

But while her muscle weakness was the most obvious sign of a problem, Lilly had cognitive issues too. The family pediatrician referred her to a hospital in New Hampshire, about two hours east of their home in central Vermont. Doctors there diagnosed Lilly with global developmental delay, often a precursor to intellectual disability.

https://answers.childrenshospital.org/new-genetic-test-yields-answers/

A new kind of genetic test

Dr. Srivastava had a few thoughts about what might be causing Lilly's condition. He took blood samples and ordered tests. They came back negative. But when Lilly returned six months later for a check-up, he suggested a kind of genetic testing called exome sequencing, which scans the most important part of a person's genetic code for errors.

"In the last few years," Dr. Srivastava says, "we've been turning more and more to exome sequencing, because it's much better than older sequencing technologies at finding small errors in genes that can have big consequences for patients like Lilly."

https://answers.childrenshospital.org/new-genetic-test-yields-answers/

Two weeks later, Kate and her mother, a hospital nurse, met with Dr. Srivastava and got the answer the Cole family been pursuing for a decade. Lilly had been born with a mutation in a gene called *SETD5*, which is located on chromosome 3. The resulting condition, discovered only five years ago, has all the symptoms Lilly had been living with since birth. Finally, it all made sense.

https://answers.childrenshospital.org/new-genetic-test-yields-answers/

Between March 3rd, 2015 and December 9th, 2021:

<u>118</u> individuals at GeneDx were diagnosed with pathogenic variants in *SETD5*

Between March 3rd, 2015 and December 9th, 2021:

<u>118</u> individuals at GeneDx were diagnosed with pathogenic variants in *SETD5*

Positive cases in 33k autism spectrum retrospective review

- 5331 individuals with LPATH/PATH in causative genes (16.1%)
- 1021 different genes
- 482 genes only had one variant/individual
- 338 genes were not in GeneDx's expanded Autism/ID panel (2771 genes)

Gene	Frequency
ARID1B	102
SHANK3	101
MECP2	98
SCN2A	89
ANKRD11	83
PTEN	72
SYNGAP1	62
CHD8	59
KMT2A	59
DDX3X	54

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Finding your group

GeneDx
an OPKO Health Company

207 Perry Parkway, Gaithersburg, MD 20877
Phone: 301-519-2100
Fax: 201-421-2010
E-mail: genedx@genedx.com
www.genedx.com

Request to Contact

Dear Physician or Genetic Counselor,

You have referred one of your patients for genetic testing to GeneDx. Based on the genetic test results, your patient may benefit from information about available support groups or be eligible to participate in a research study through an outside group. Details can be found in the attached letter. If you or your patient(s) are interested in pursuing these opportunities, please contact the respective group directly via the contact information provided in the letter.

Of note, the attached letter is of an informational nature only. While GeneDx makes every effort to ensure its accuracy, this information is not meant to endorse a particular support group or research project, nor serve as medical advice. GeneDx presents this opportunity as a courtesy to clinicians and families who may wish to obtain more details and possibly participate.

Sincerely,
Your GeneDx Team

CureARS

CureARS is a patient organization led by parents of affected children. We are dedicated to improving the lives of children and families affected by the Mitochondrial **A**minoacyl t**R**NA **S**ynthetase Disorders (ARS Genes). These disorders are neurometabolic disorders that cause a variety of Mitochondrial Diseases (Mito).

We are deeply committed to funding research, connecting & providing resources to patients, and raising awareness for these disorders. We welcome you to join our community. Please reach out directly or visit our website www.curears.org to learn more about Mitochondrial ARS Genes and our efforts.

We understand how overwhelming this diagnosis can be and are here to help you and your family!

We look forward to hearing from you!

Ashley Rowland Desiree Magee

Ashley Rowland & Desiree Magee
Founders & Parents of ARS Warriors
CureARS, A NJ Non-profit Corporation
E-mail: info@curears.org
Website: https://www.curears.org/
Facebook & LinkedIn: @curears
Instagram: @cure4ars
Facebook Support Group @ARSGeneCommunity

RARE ENTREPRENEUR
BOOTCAMP

Future

NEWS

Can gene sequencing at birth prevent terrible diseases? Researchers hope so.

Karen Weintraub
USA TODAY

Published 8:00 a.m. ET Oct. 5, 2022 | Updated 10:57 a.m. ET Oct. 5, 2022

GUARDIAN STUDY

The GUARDIAN study is a free newborn screening study to help all babies have healthier lives.

LEARN MORE

Our Partners

COLUMBIA
COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

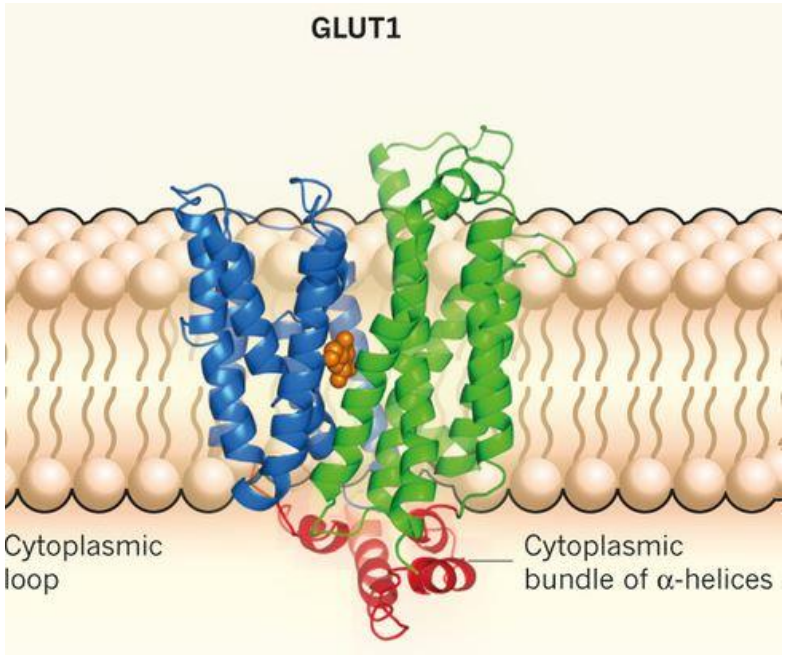
GeneDx sema4

illumina

NEW YORK STATE Department of Health

NewYork-Presbyterian

SEIZURES

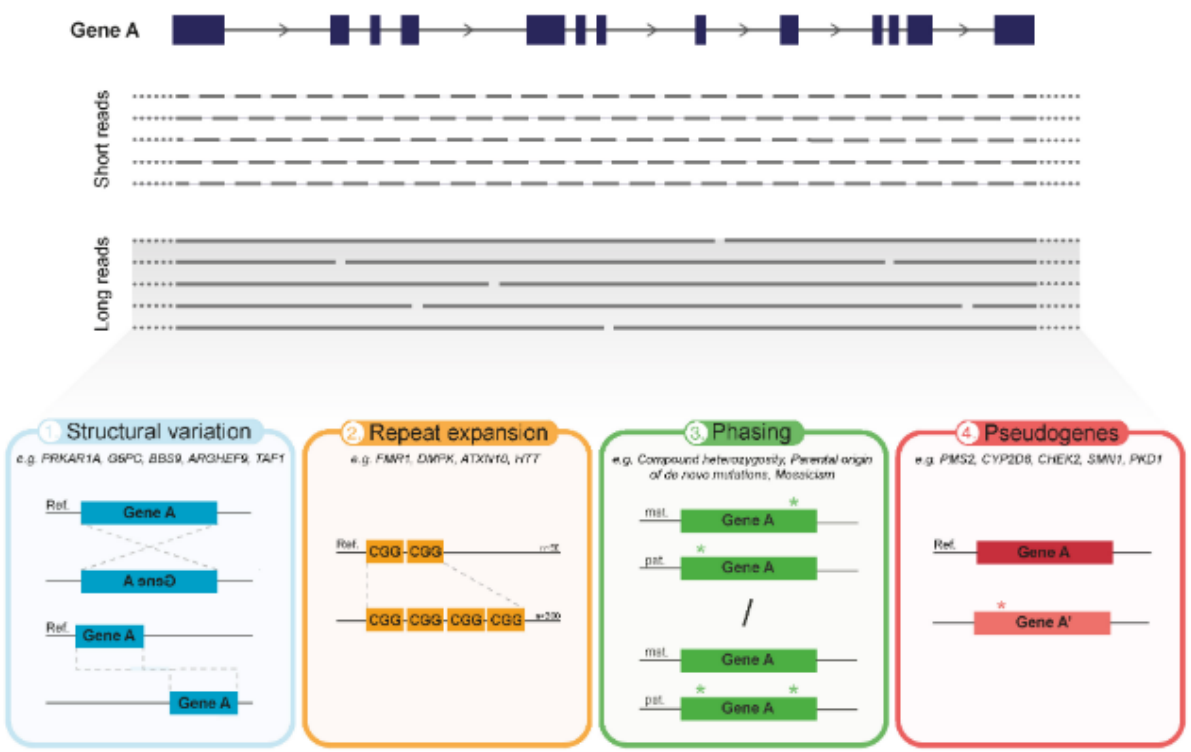


SLC2A1 Gene

Glucose Transporter Type 1 Deficiency Syndrome

- Cases at GeneDx (HPO: seizure/epilepsy) = 77
- Average age 9.9 years
- Median age 7 years

Long Read Sequencing



Mantere T, Kersten S and Hoischen A (2019) Long-Read Sequencing Emerging in Medical Genetics. Front. Genet. 10:426. doi: 10.3389/fgene.2019.00426

Thank You!

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