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Melbourne Genomics
Health Alliance

Global knowledge. Individual care.

Introducing Genomics

Fran Maher

Education Officer,
Melbourne Genomics Health Alliance

Alliance members

The Royal Melbourne Hospital
The Royal Children's Hospital Melbourne
The University of Melbourne
Walter+Eliza Hall Institute of Medical Research
murdoch children's research institute
CSIRO
agrf
Peter Mac Peter MacCallum Cancer Centre Victoria Australia
Austin Health
MonashHealth

Supported by

VICTORIA State Government

Genome

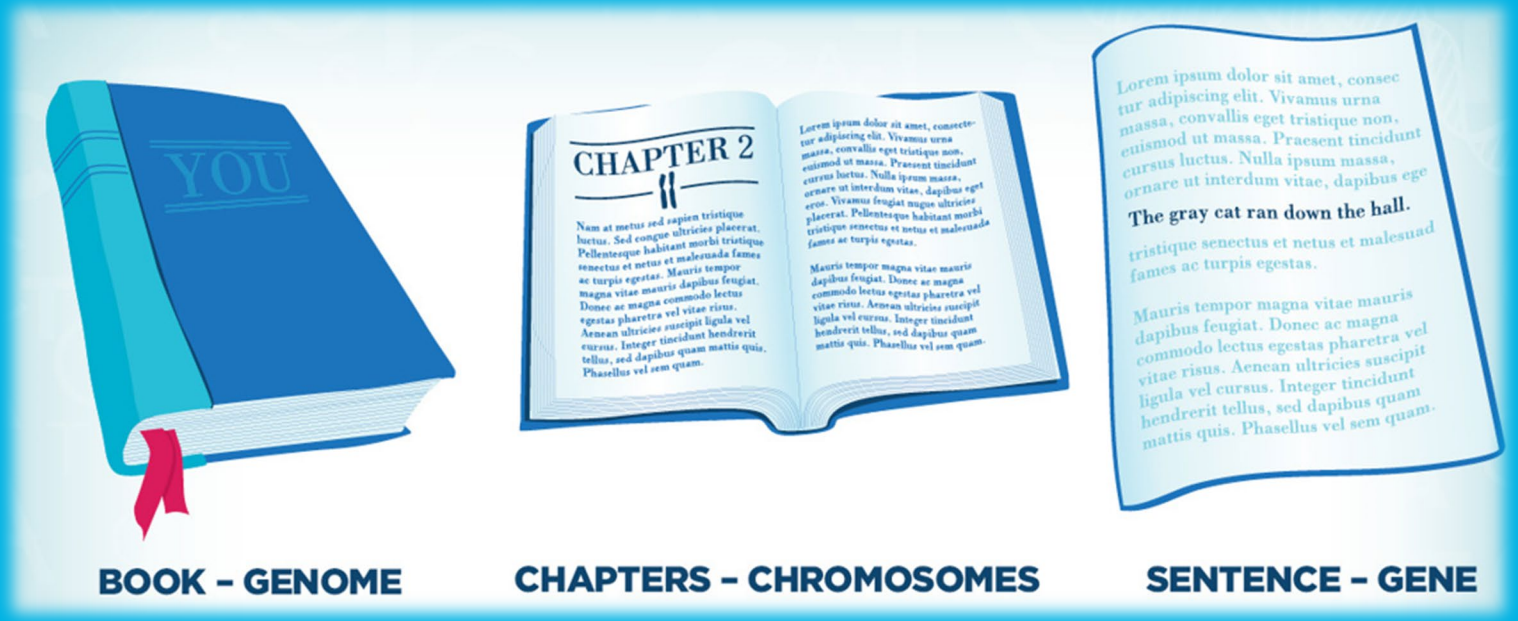
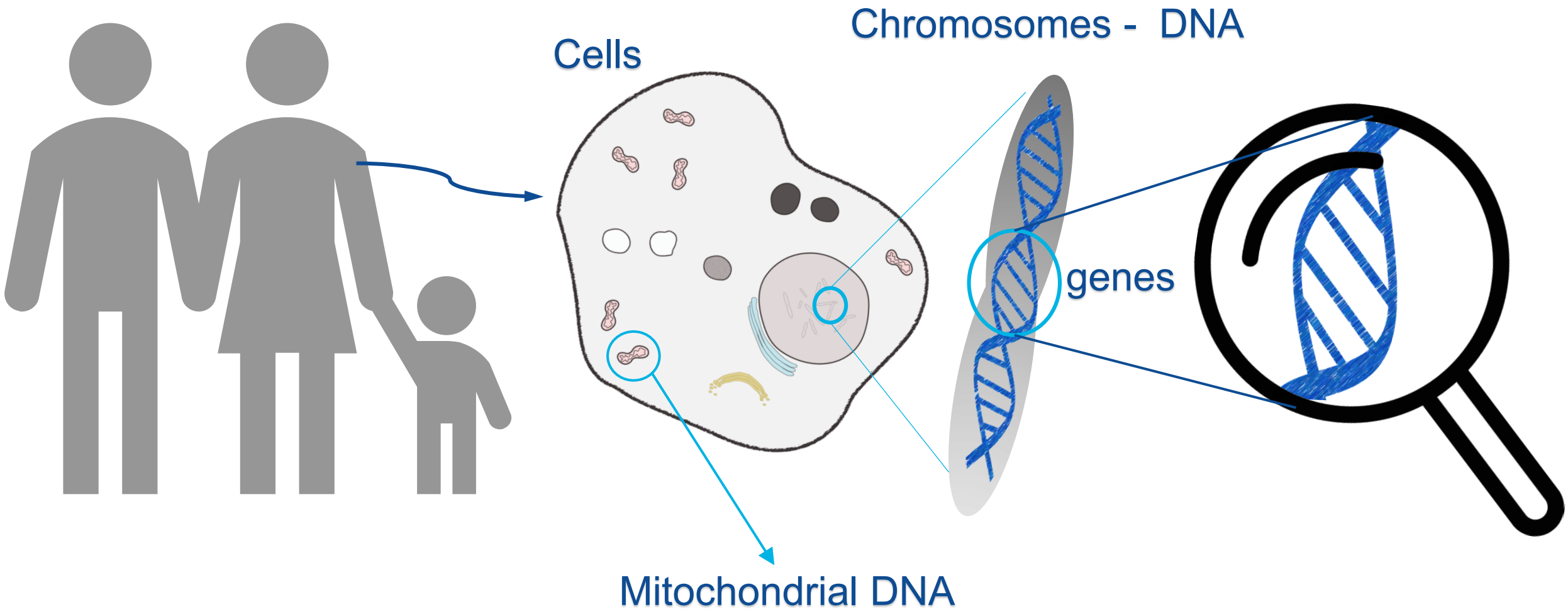
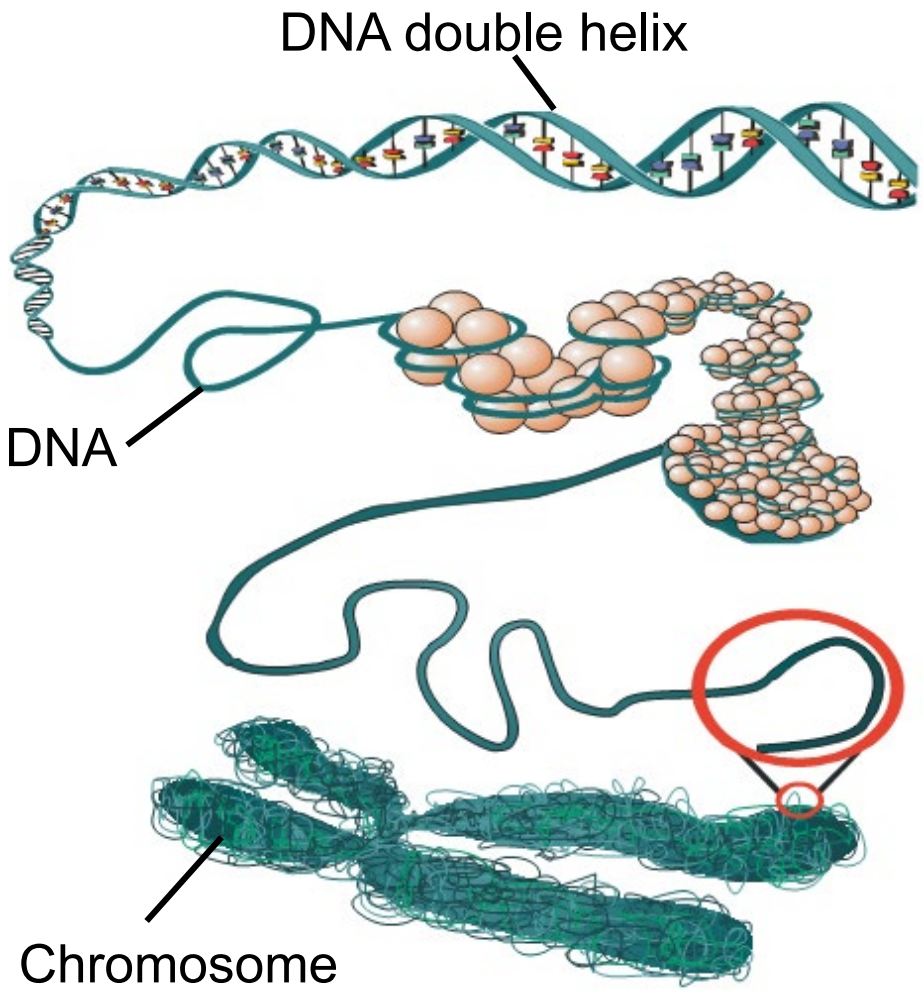


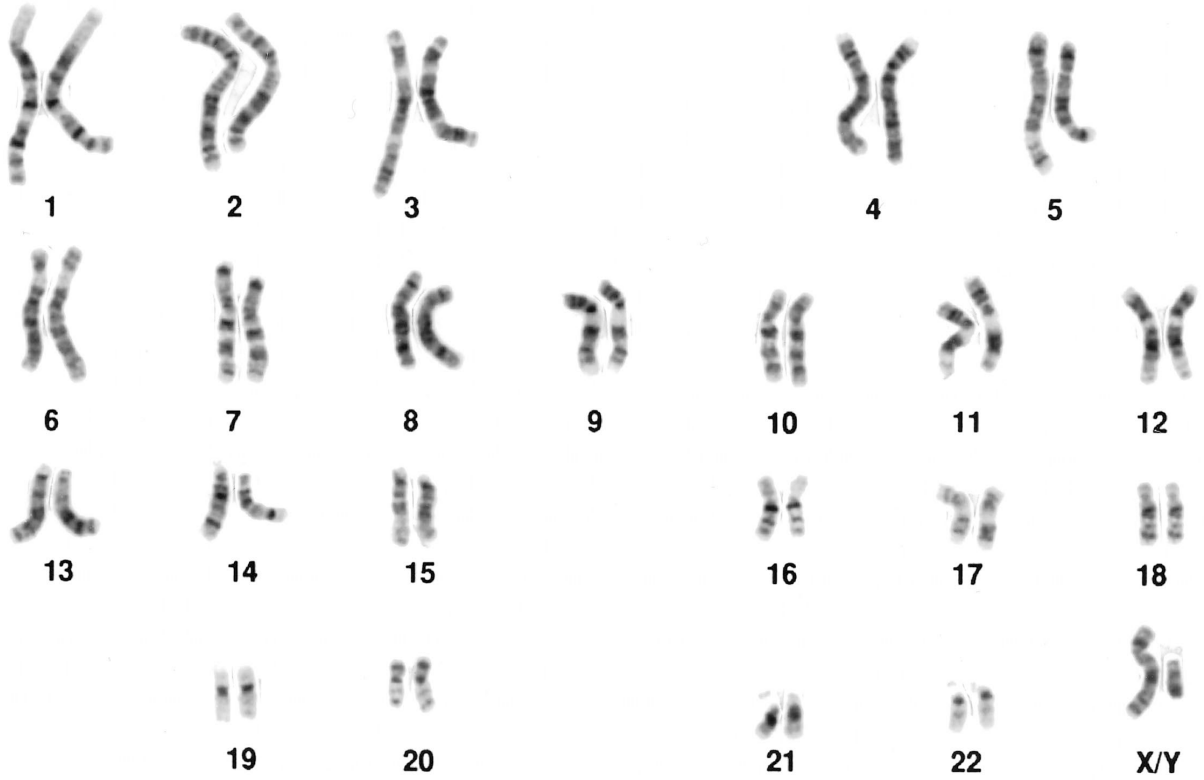
Image: National Society of Genetic Counselors

Your genome



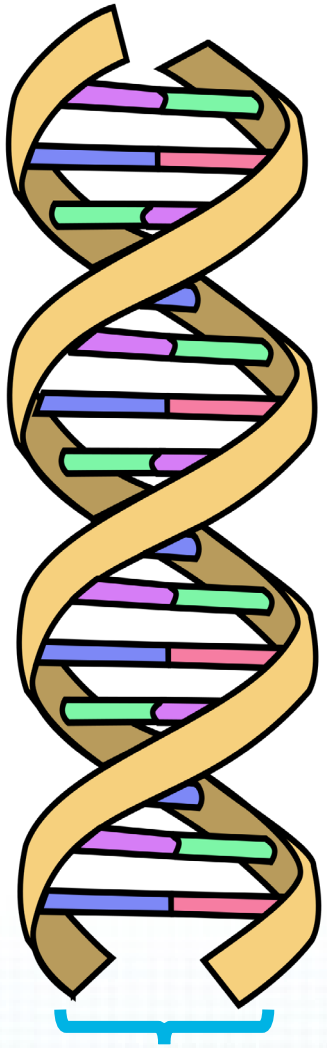
Chromosomes



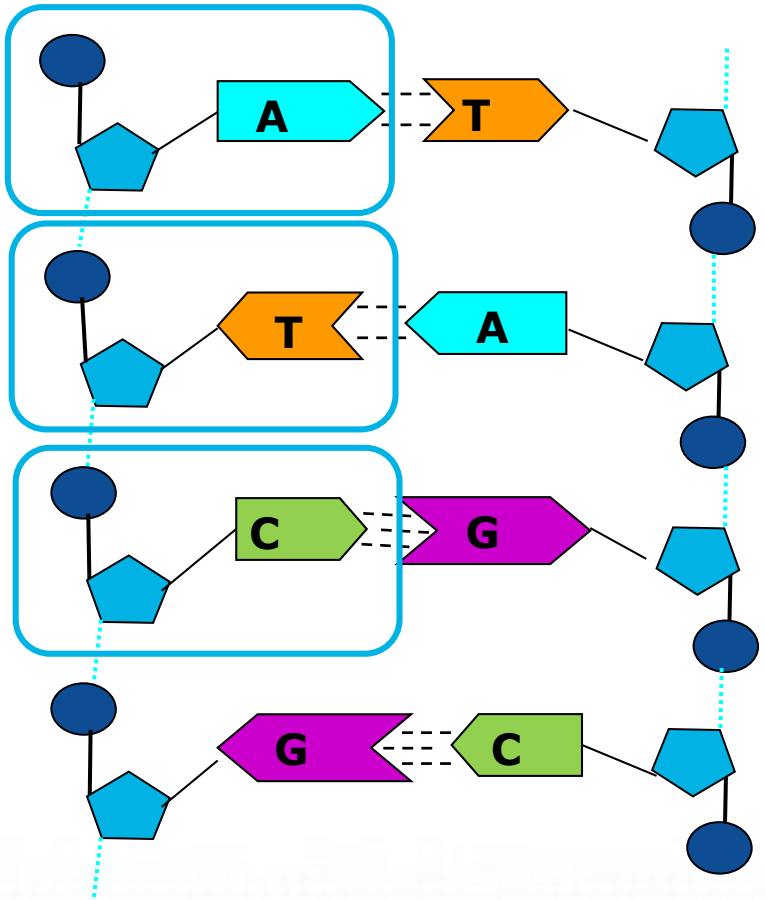


46 chromosomes
(2 sets of 23 chromosomes)

DNA double helix is built of nucleotides



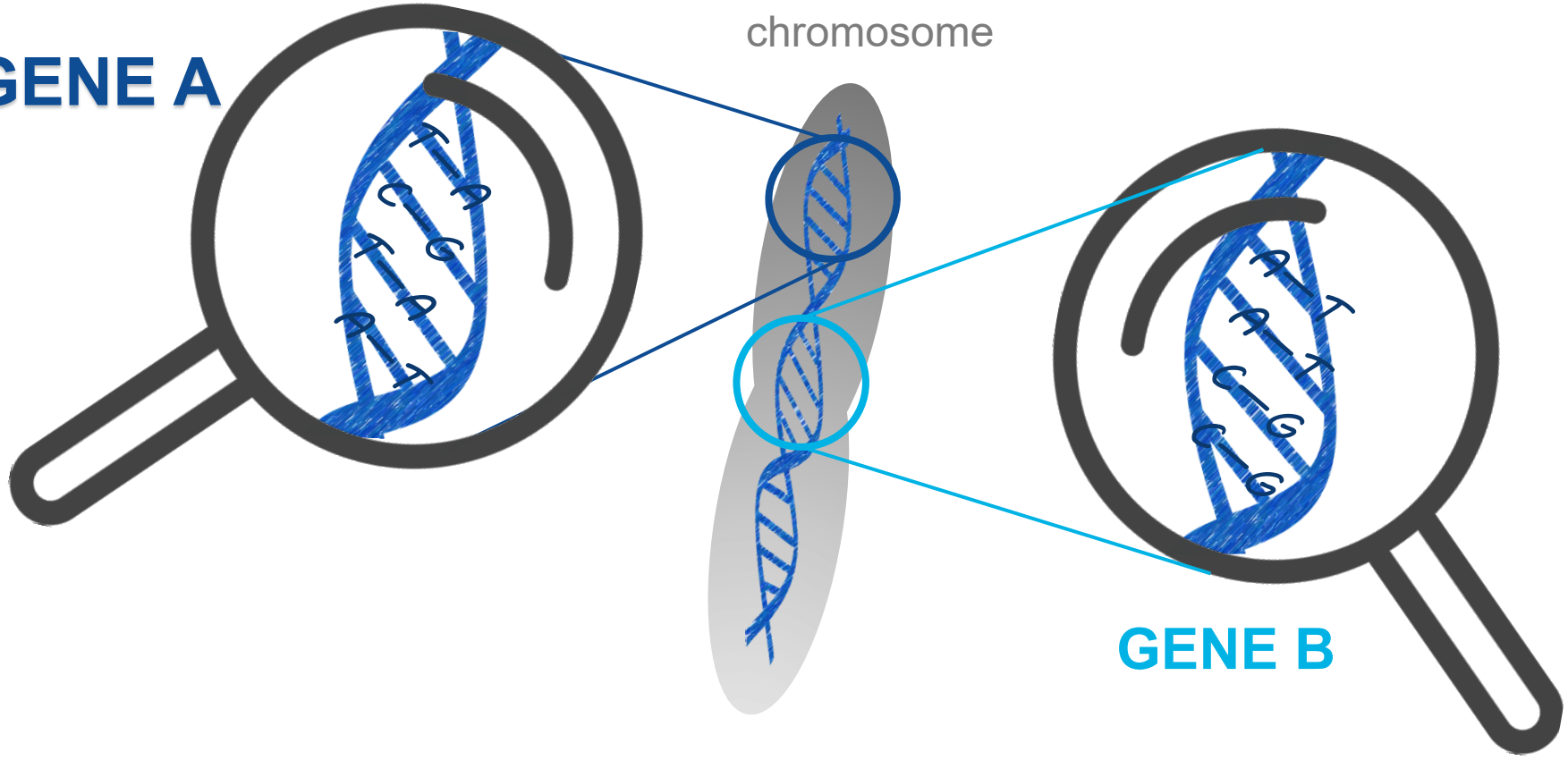
Complementary base pairs



3 billion "letters" of DNA

Genes

Recipes for proteins



~22,000 genes

Only 1-2% of the whole genome carries the code for proteins

The protein coding section is called the exome

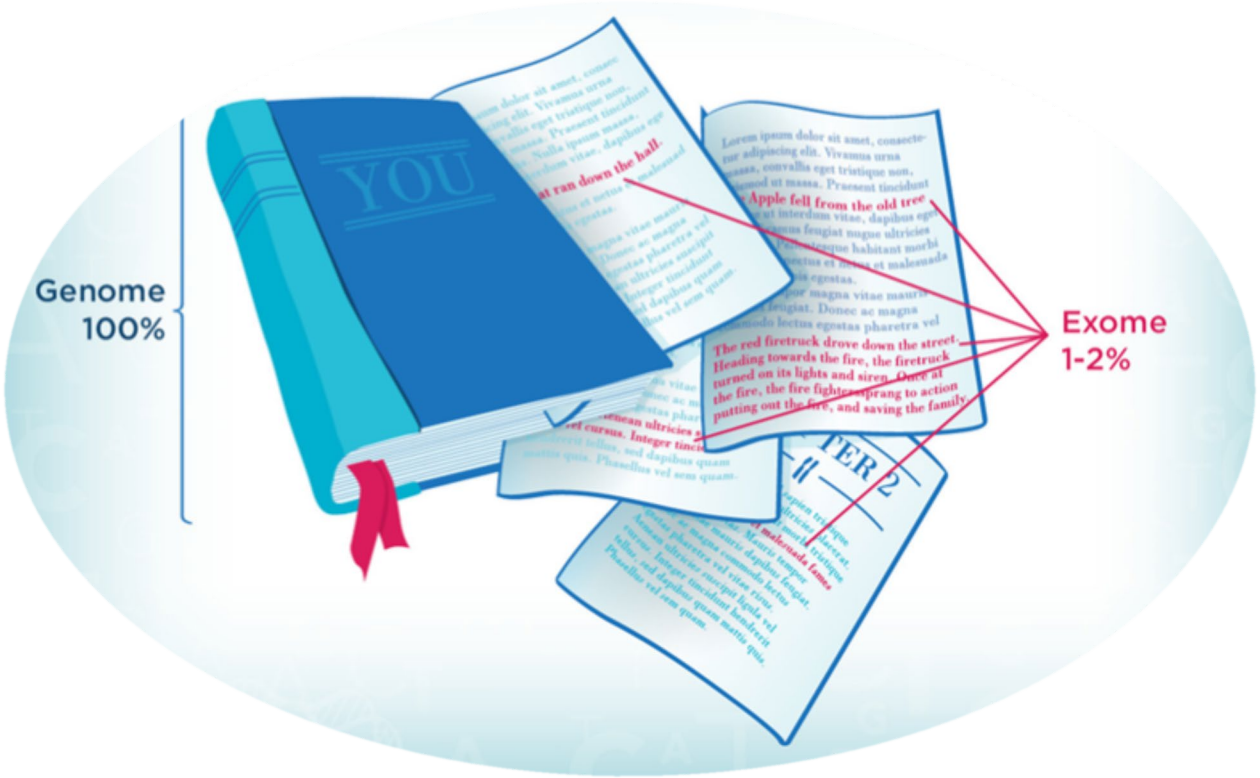


Image: adapted from National Society of Genetic Counselors

Gene sequence – human keratin

```
   1  cactcaaggt gtgcaggcag ctgtgtttgt caggaaggca gaaggagttg gctttgcttt aggggaggag acgaggtccc acaacaccct ctgaagggta tataaggagc cccagcgtgc
 121  agcctggcct ggtacctcct gccagcatct cttgggtttg ctgagaactc acgggctcca gctacctggc catgaccacc acatttctgc aaacttcttc ctccaccttt gggggtggct
 241  caacccgagg gggttccctc ctggctgggg gaggtggctt tggtgggggg agtctctctg ggggaggtgg aagccgaagt atctcagctt cttctgctag gtttgtctct tcagggtcag
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 481  atggtggtct cctctctggc aatgagaaaa ttaccatgca gaacctcaat gaccgcctgg cctcctacct ggacaaggta cgtgccctgg aggaggccaa tgctgacctg gaggtgaaga
 601  tccatgactg gtaccagaag cagaccccaa ccagcccaga atgcgactac agccaatact tcaagaccat tgaagagctc cgggacaaga tcatggccac caccatcgac aactcccggg
 721  tcatcctgga gatcgacaat gccaggctgg ctgcggacga cttcaggctc aagtatgaga atgagctggc cctgcgccag ggcgttgagg ctgacatcaa cggcttgcgc cgagtcctgg
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1321 agctccgatg cgagatggag gctcagaacc aggagtacaa gatgctgctt gacataaaga cacggctgga gcaggagatc gctacttacc gcagcctgct cgagggccag gatgccaaga
1441 tggctggcat tggcatcagg gaagcctctt caggaggtgg tggtagcagc agcaatttcc acatcaatgt agaagagtca gtggatggac aggtggtttc ttcccacaag agagaaatct
1561 aagtgtctat tgcaggagaa acgtcccttg ccactcccca ctctcatcag gccaagtgga ggactggcca gagggcctgc acatgcaaac tccagtccct gccttcagag agctgaaaag
1681 ggtccctcgg tcttttattt cagggctttg catgcgctct attccccctc tgcctctccc caccttcttt ggagcaagga gatgcagctg tattgtgtaa caagctcatt tgtacagtgt
1801 ctgttcatgt aataaagaat tacttttcct tttgcaaata aaaaaaaaaa aaaaaaaaaa a
```
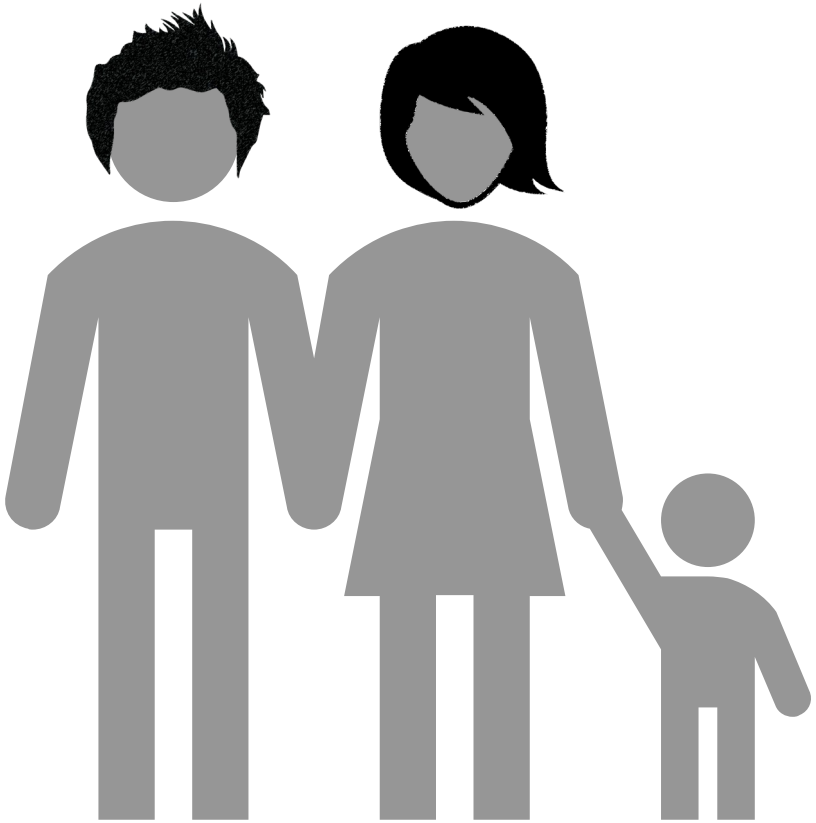
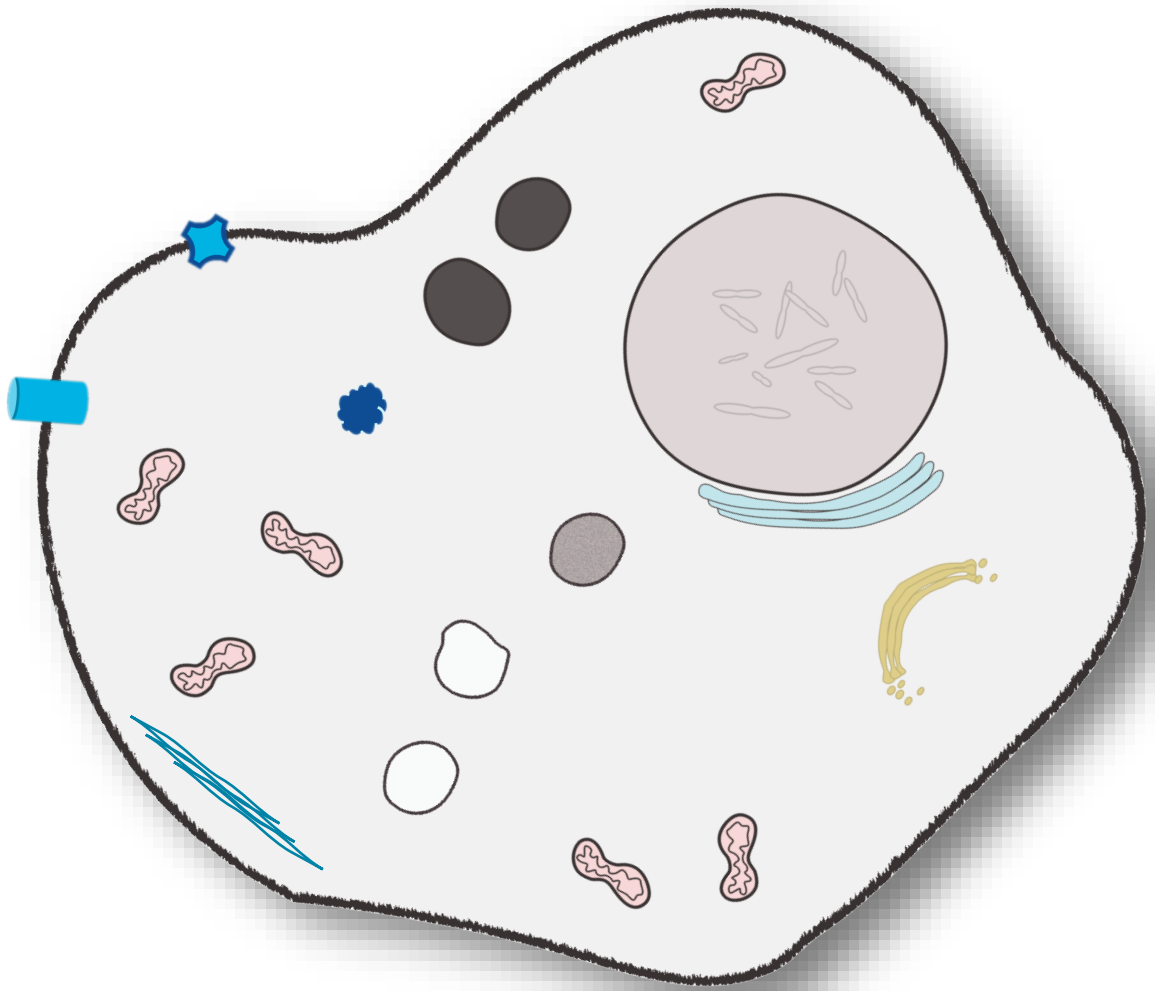

1861 coding bases

Proteins are …

The molecules that give us our characteristics





EXTRA DETAIL

Genes ‘turn on’ and ‘turn off’

Genes are ‘turned on’ to produce protein only when needed

- ***Different genes are turned on at different times during development***
- ***Different genes are turned on in different cell and tissues***
- ***A gene variant might affect only some cells and tissues***

‘Regulator’ genes act as ON-OFF switches

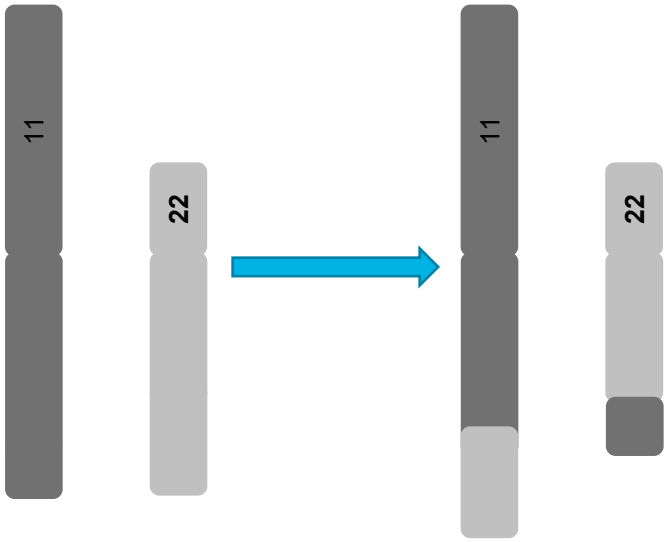
- ***Variants in the regulators can change how other genes are turned on or off***

Genetic variants

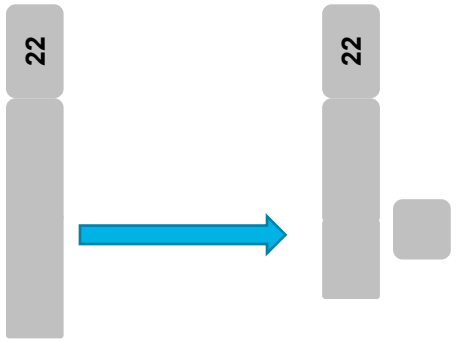
Single nucleotide variants

```
Patient  :attgccttgggatccctgtccttagtccttt ttaacatgtagctttatcgatcgtagct
Reference:atttccttgggatgcctgtcctaagtcctttcttaacatgtagctatcgatcgtagct
```

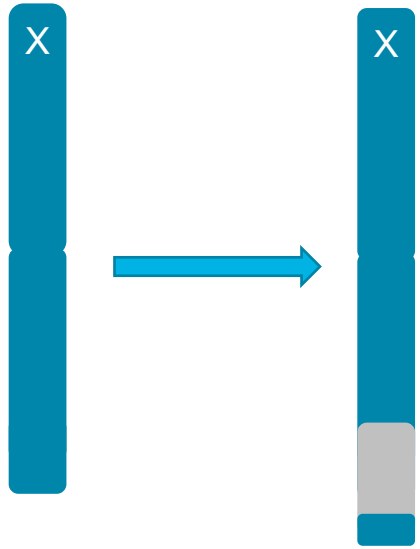
Chromosome variants



translocation

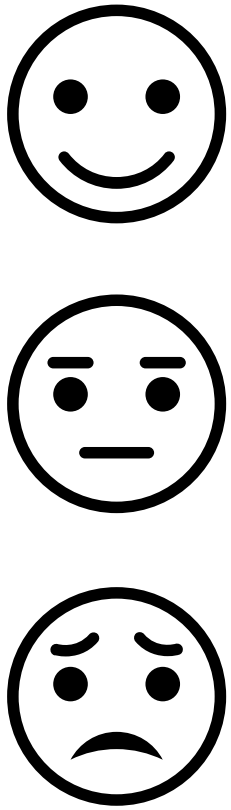


deletion



expansion

Variants can be …



… depending on how they affect the proteins in your cells

Variants can be…

benign

Normal variations in genes - not linked to disease

variant of uncertain significance (VUS)

Not certain whether it is the cause of disease

pathogenic

Some variants cause or increase risk of inherited disease

Some variants lead to cancer

Variant Curation

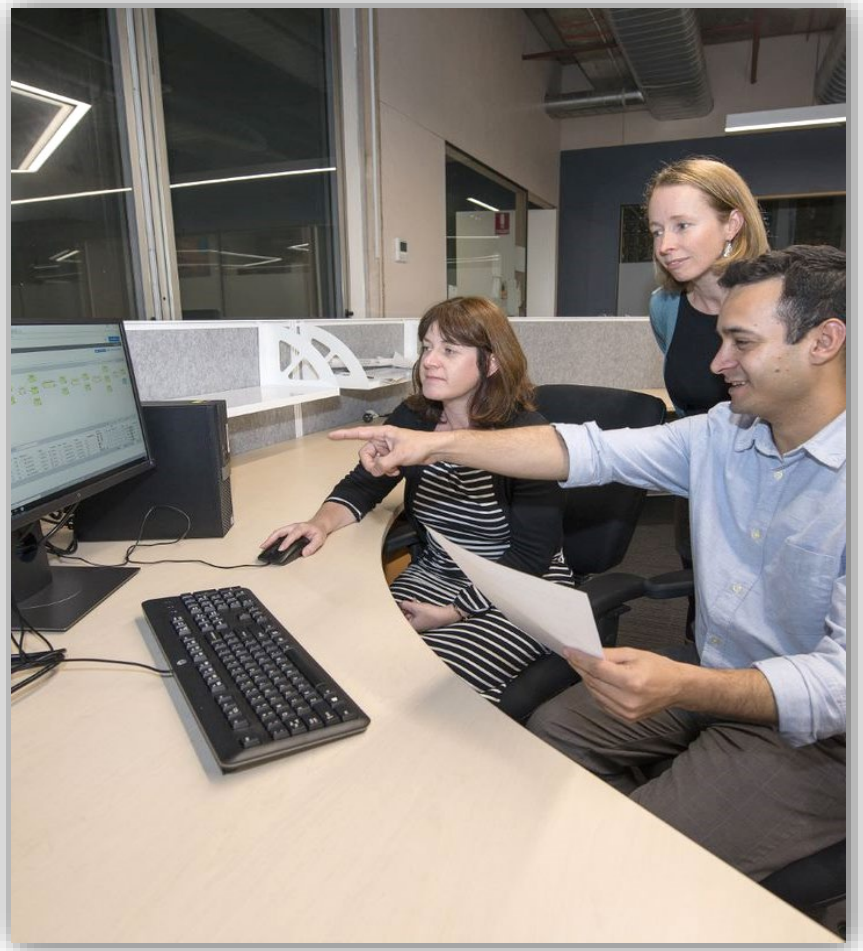
Identify and classify variants

Extract DNA → Sequence the DNA

Compare patient DNA to reference sequence

Identify & classify variants

Clinical action



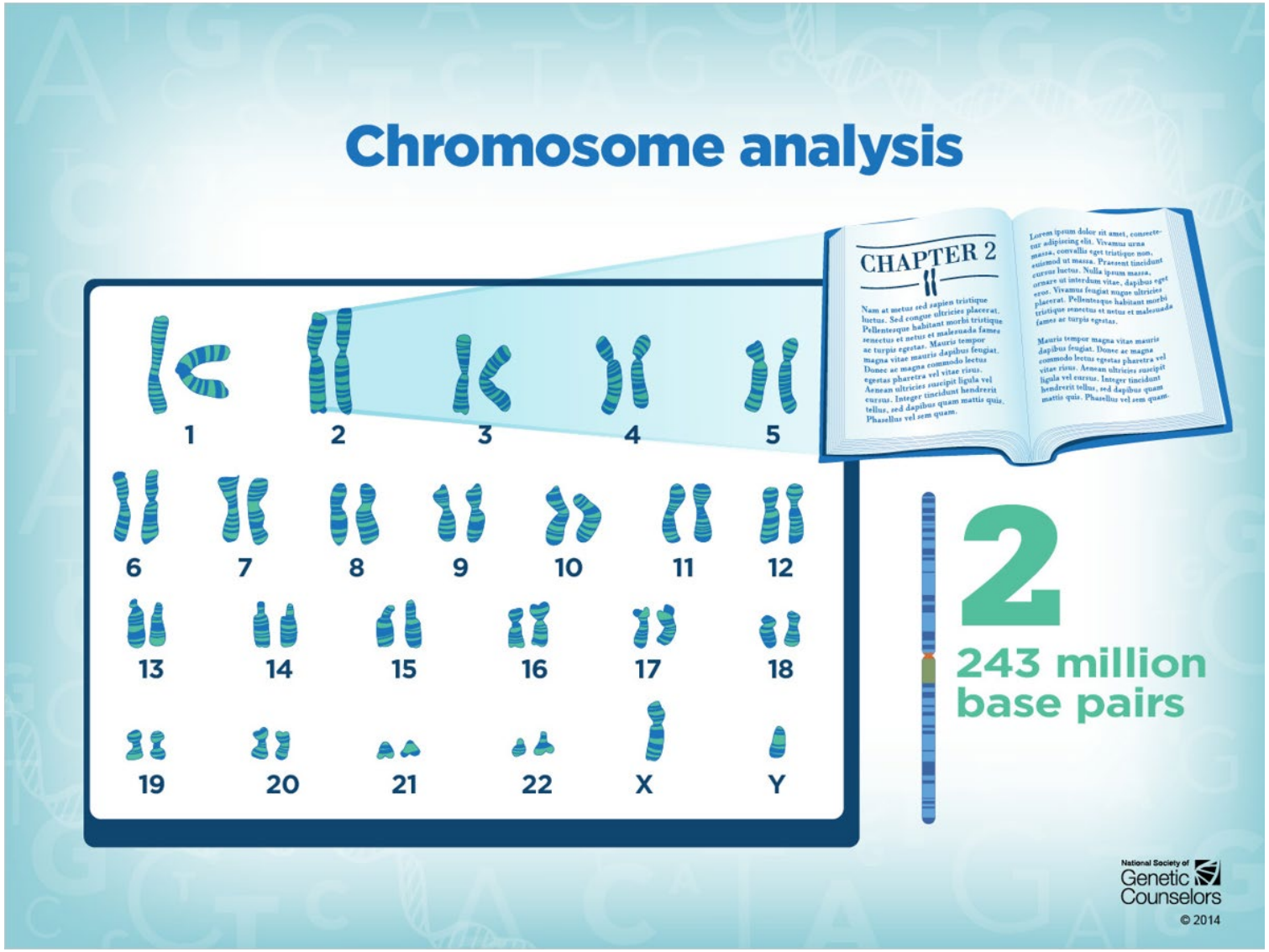
Testing for genetic variants

Karyotyping

Changes in chromosome number

Examples:

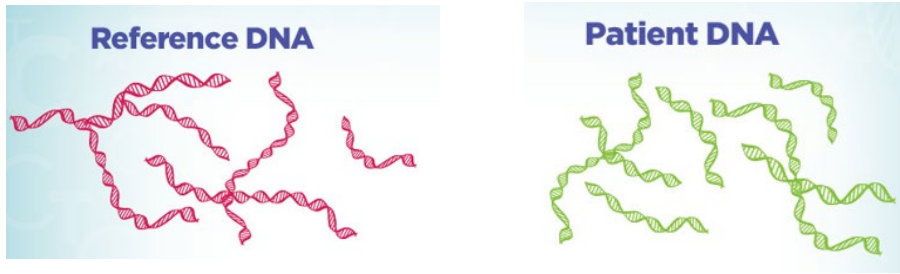
- **Down syndrome (trisomy 21)**
- **Kleinfelter syndrome (XXY)**
- **Turner syndrome (XO)**



Chromosome Microarray

Finds large deletions & duplications within chromosomes

Compare
reference & patient DNA



detect

- extra patient DNA
- same amount of DNA
- missing patient DNA

Examples:

common & unknown chromosome change

- **Di George syndrome (deletion)**
- **Intellectual disability**
- **Developmental concerns**

Single gene test

Identify genetic disease caused by variants in a single gene

Examples:

Cystic fibrosis - CFTR gene

Huntington disease - HTT gene

Haemochromatosis – HFE gene

Image: adapted from National Society of Genetic Counselors

Gene panel test

Multiple genes known to be associated with a particular type of disorder

Examples:

- **Breast cancer susceptibility BRCA1, BRCA2 + 12 other genes**
- **Cardiomyopathy – 62 gene panel**

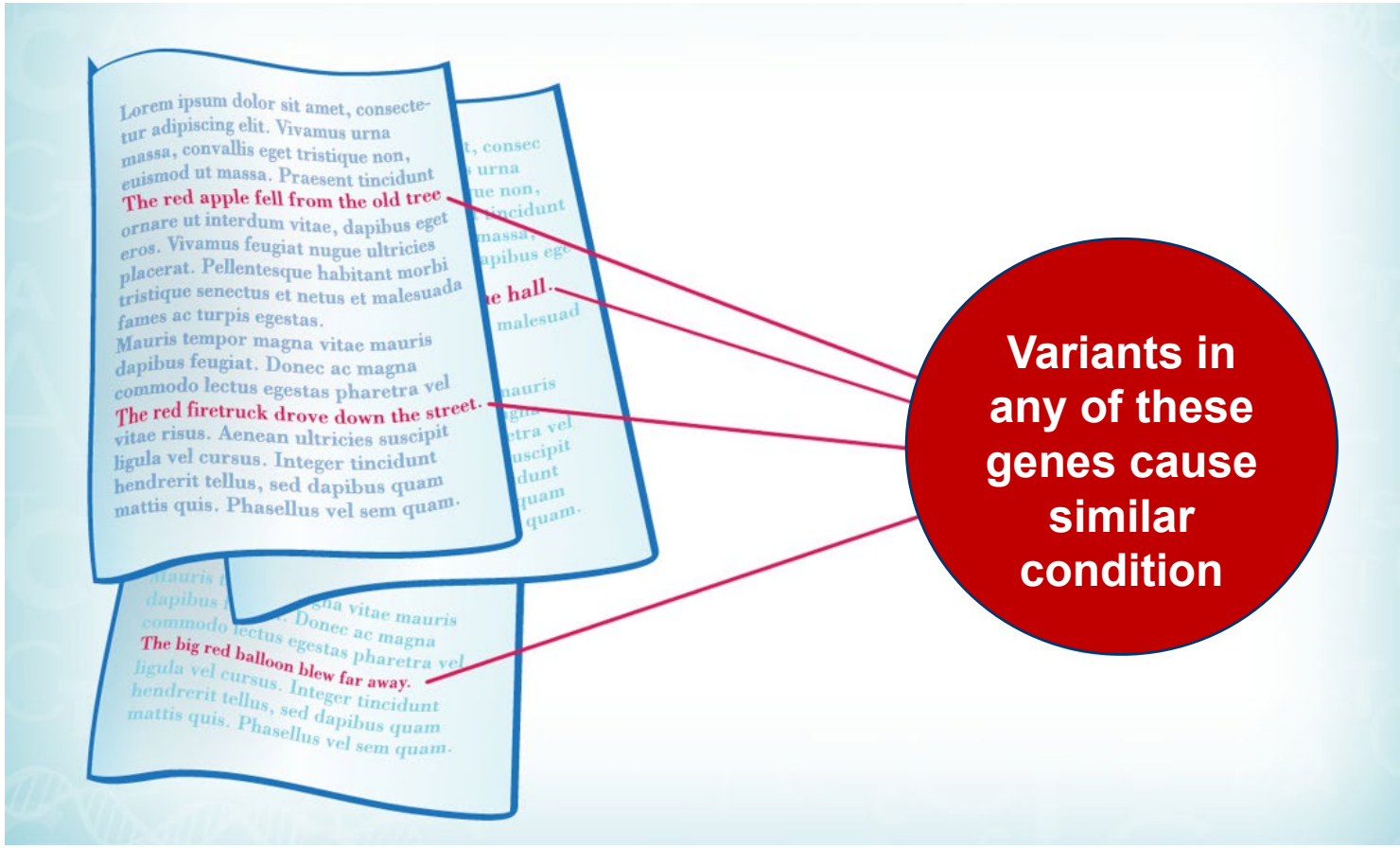


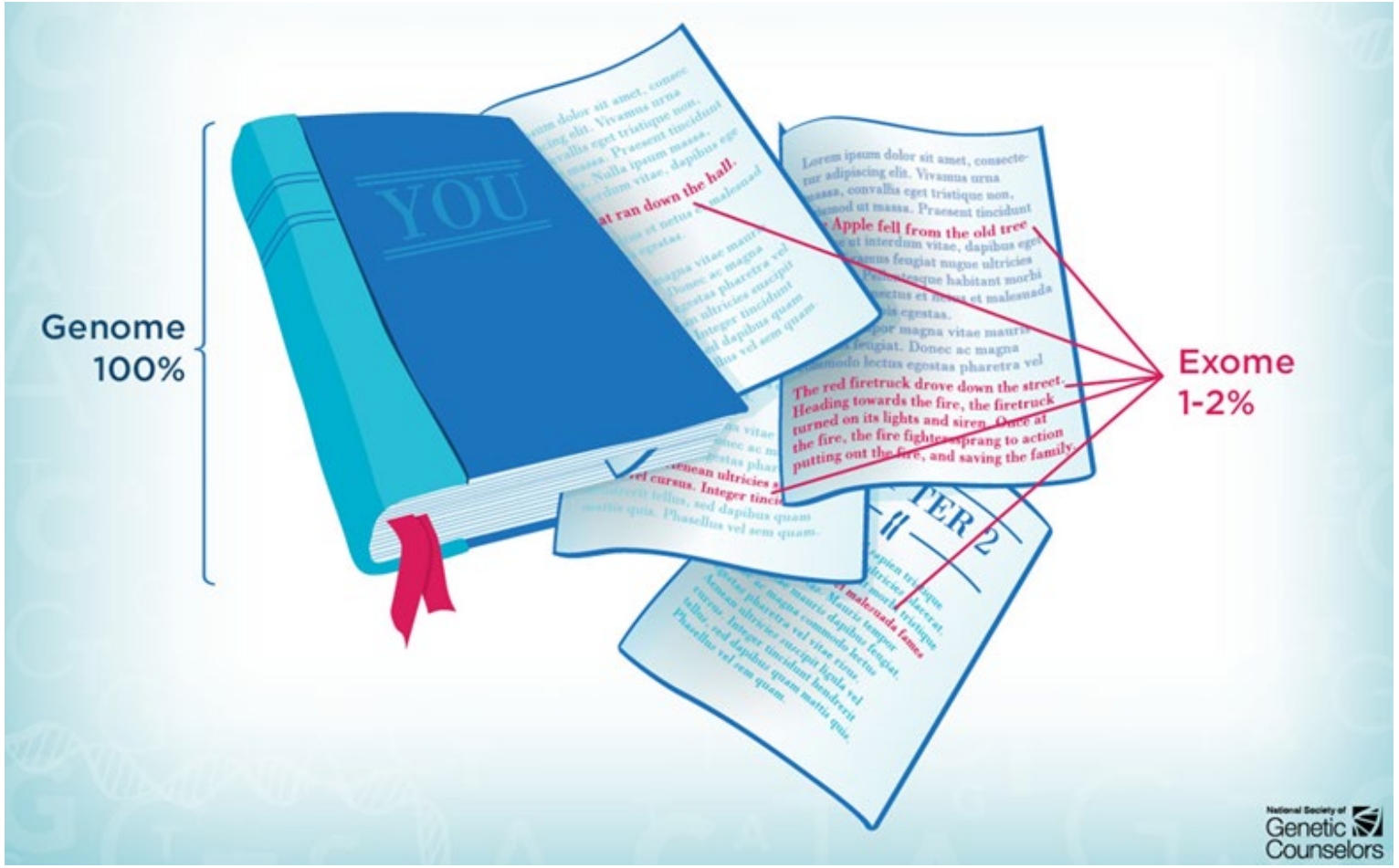
Image: adapted from National Society of Genetic Counselors

Whole exome sequencing (WES)

Reading 1-2% of the book

Reading the edited sentences

i.e. the protein-coding sections

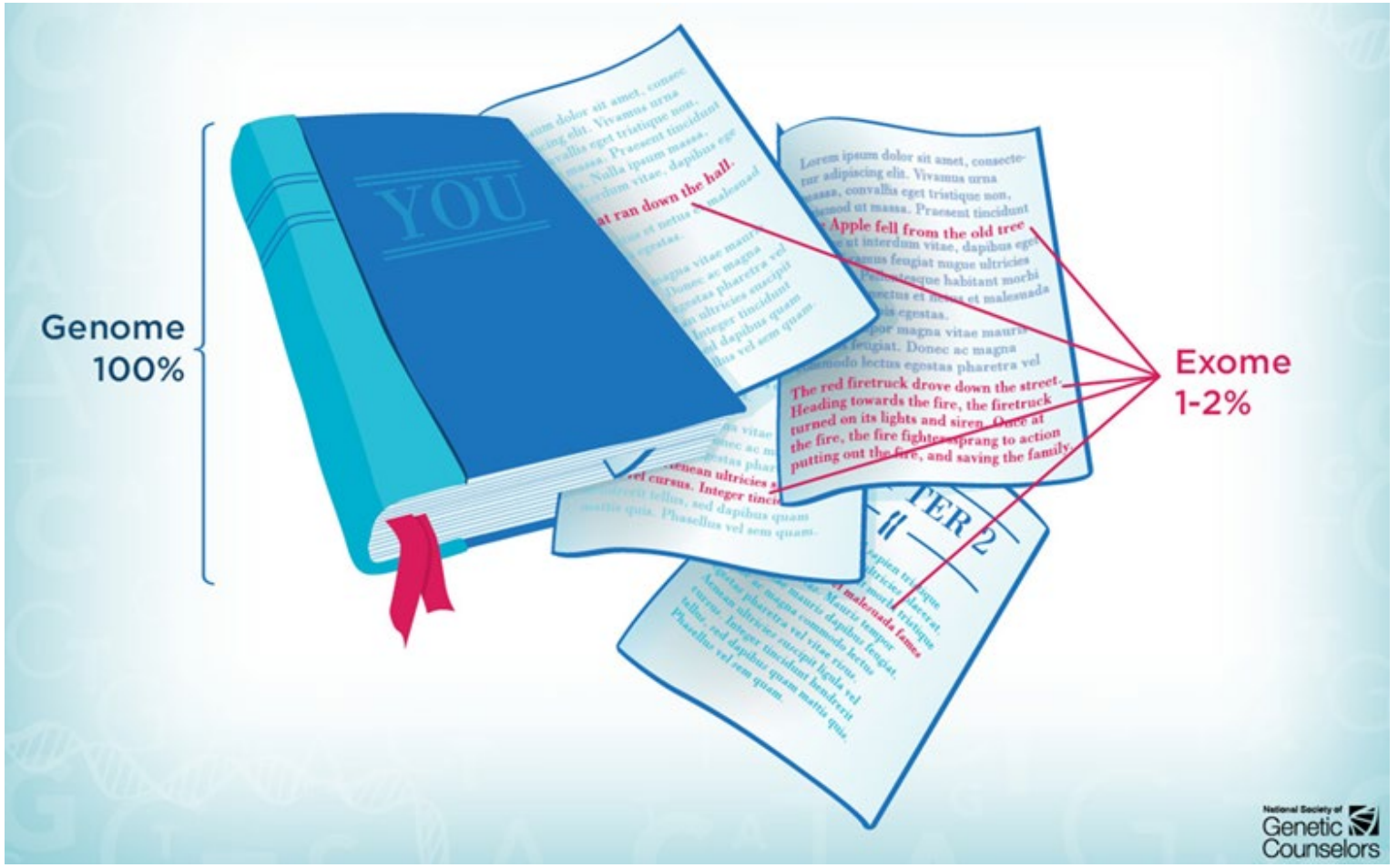


Diagnosis of:

- Rare
- Complex
- Syndromes
- Previously undiagnosed

Whole genome sequencing (WGS)

Reading the whole book



Diagnosis of:

- Rare
- Complex
- Syndromes
- Previously undiagnosed

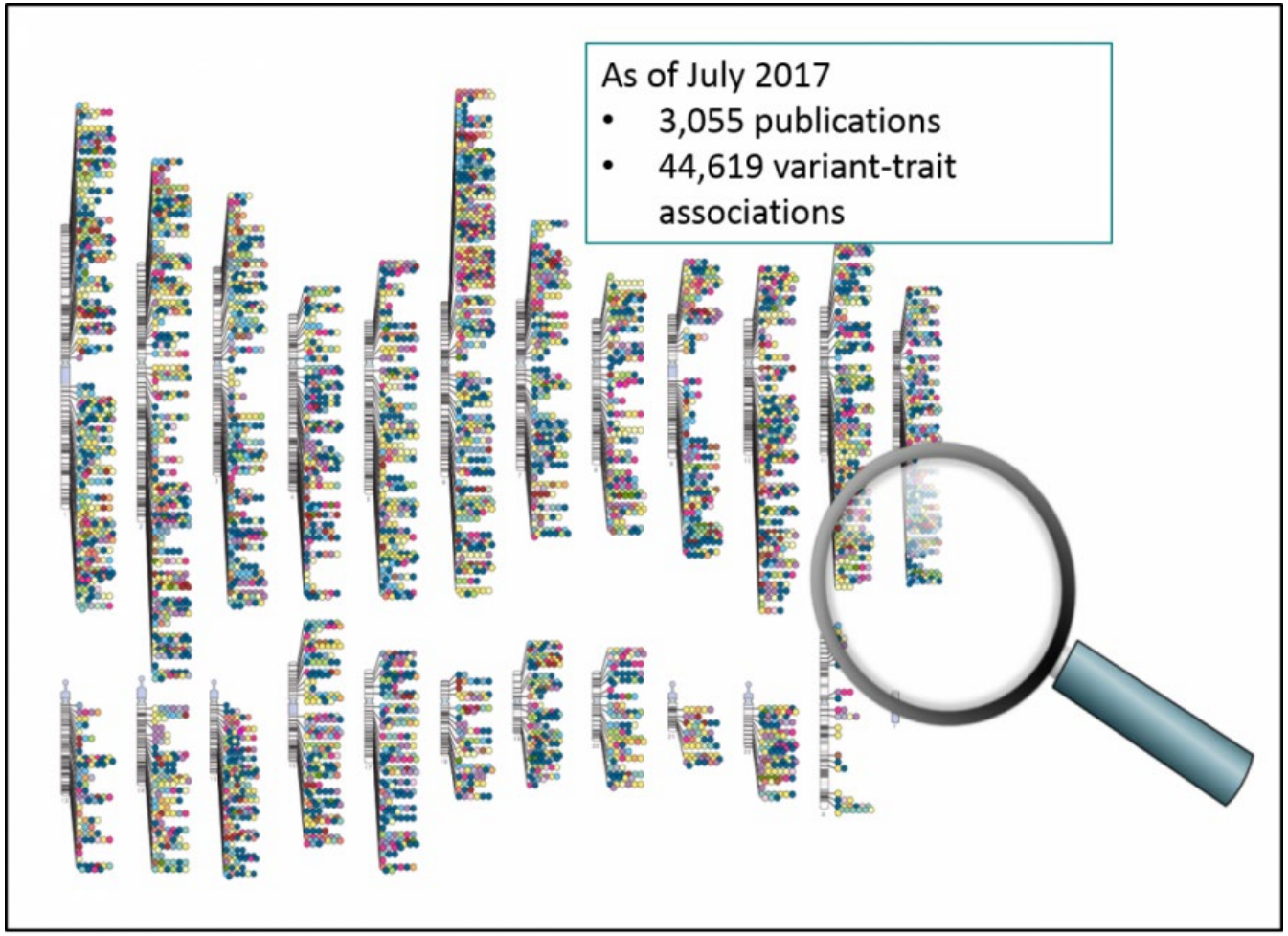
GWAS

Genome Wide Association Study

Association between common variants (SNPs) and traits

Examples:

- Common traits – hair colour/type, height
- Complex traits – height, IQ, behaviour
- Ancestry – ethnicity
- Multifactorial conditions – obesity, aging
- Disease risk – diabetes, heart disease
- Response to medication - antidepressants



The NHGRI-EBI GWAS Catalog is a publicly available resource of Genome Wide Association Studies (GWAS) and their results

Source NHGRI-EBI GWAS Catalog

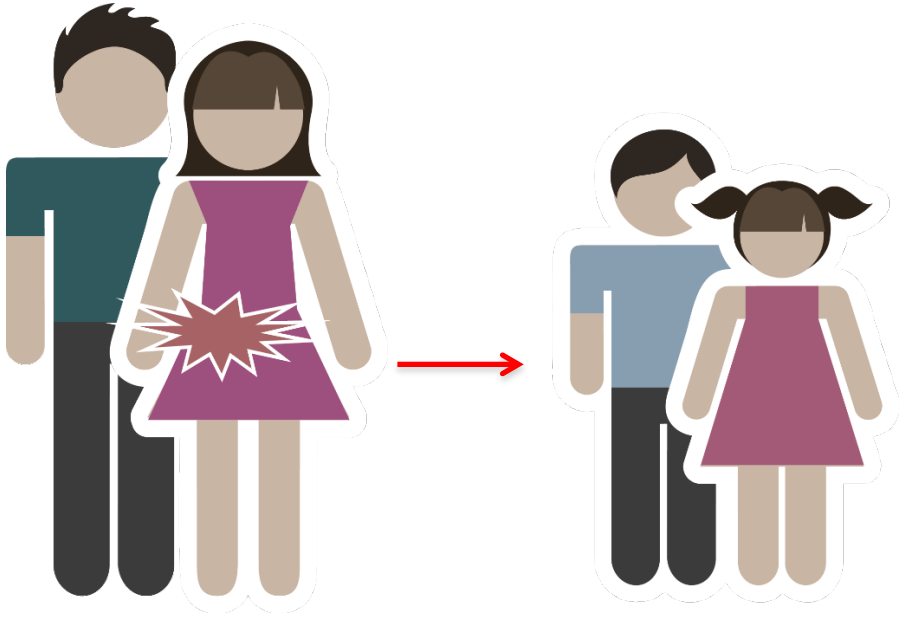
Inheriting genetic characteristics

Germline vs Somatic variants

Germline variants are inherited

Present in egg or sperm

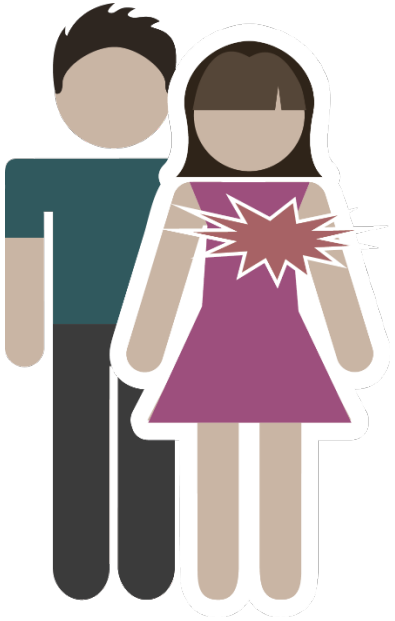
Some cause family cancer syndrome



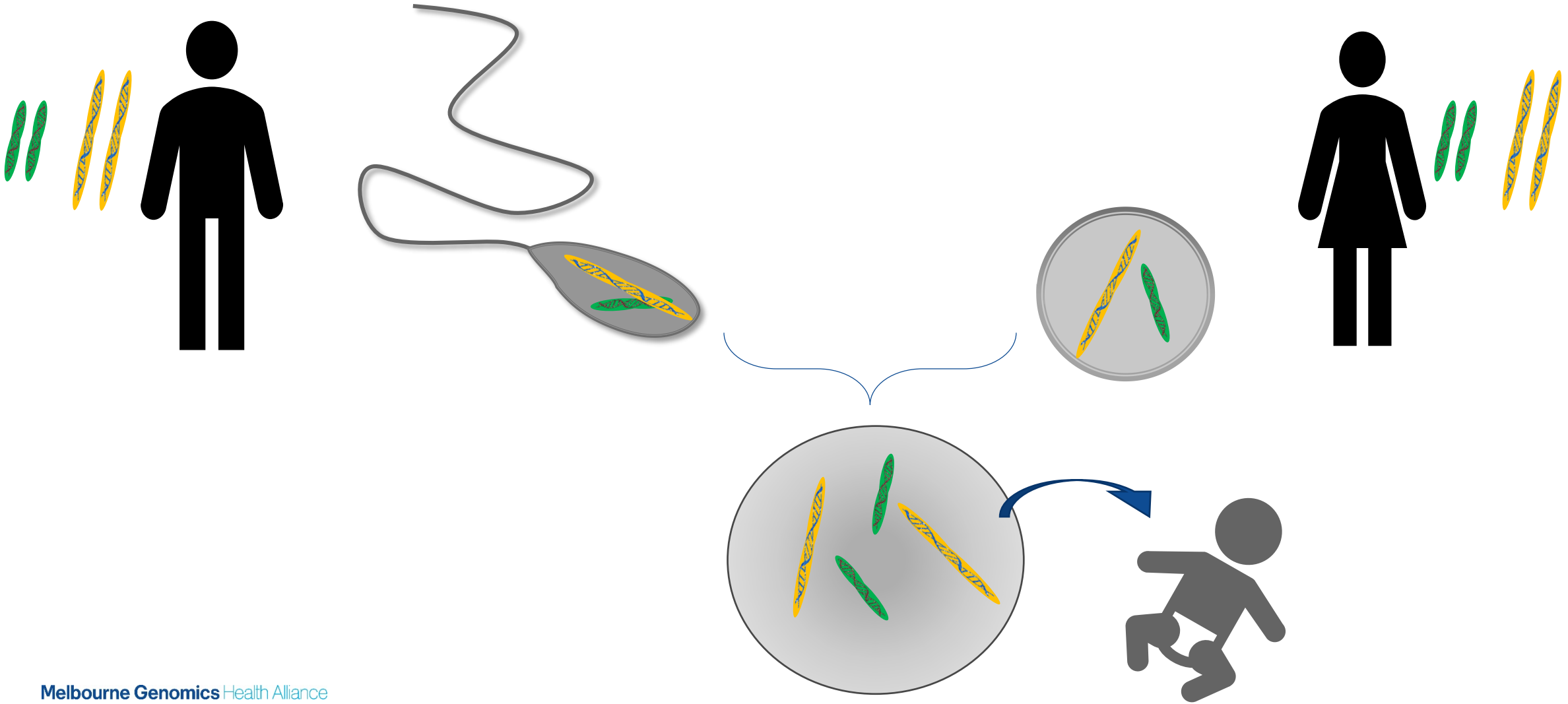
Somatic variants are not inherited

Occur in body tissues

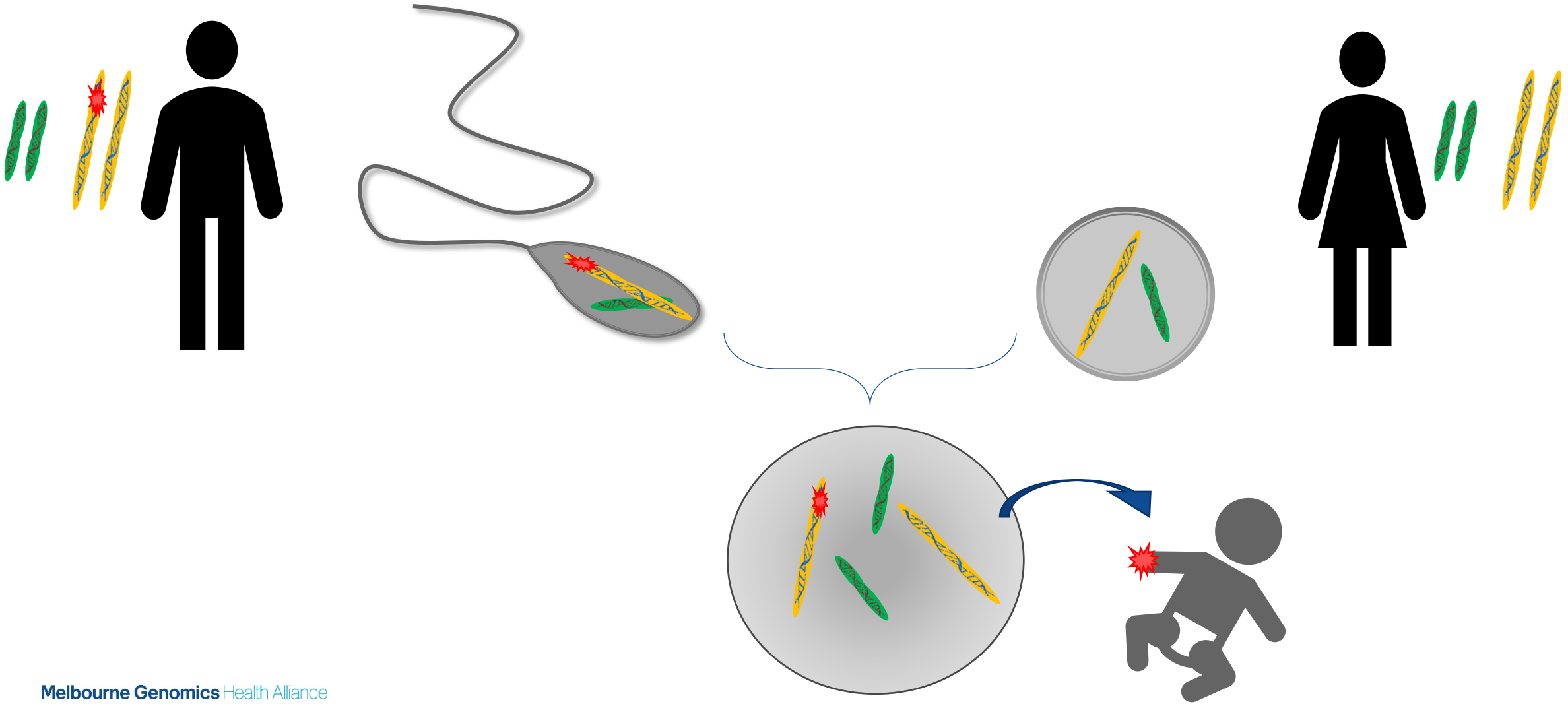
May cause cancer



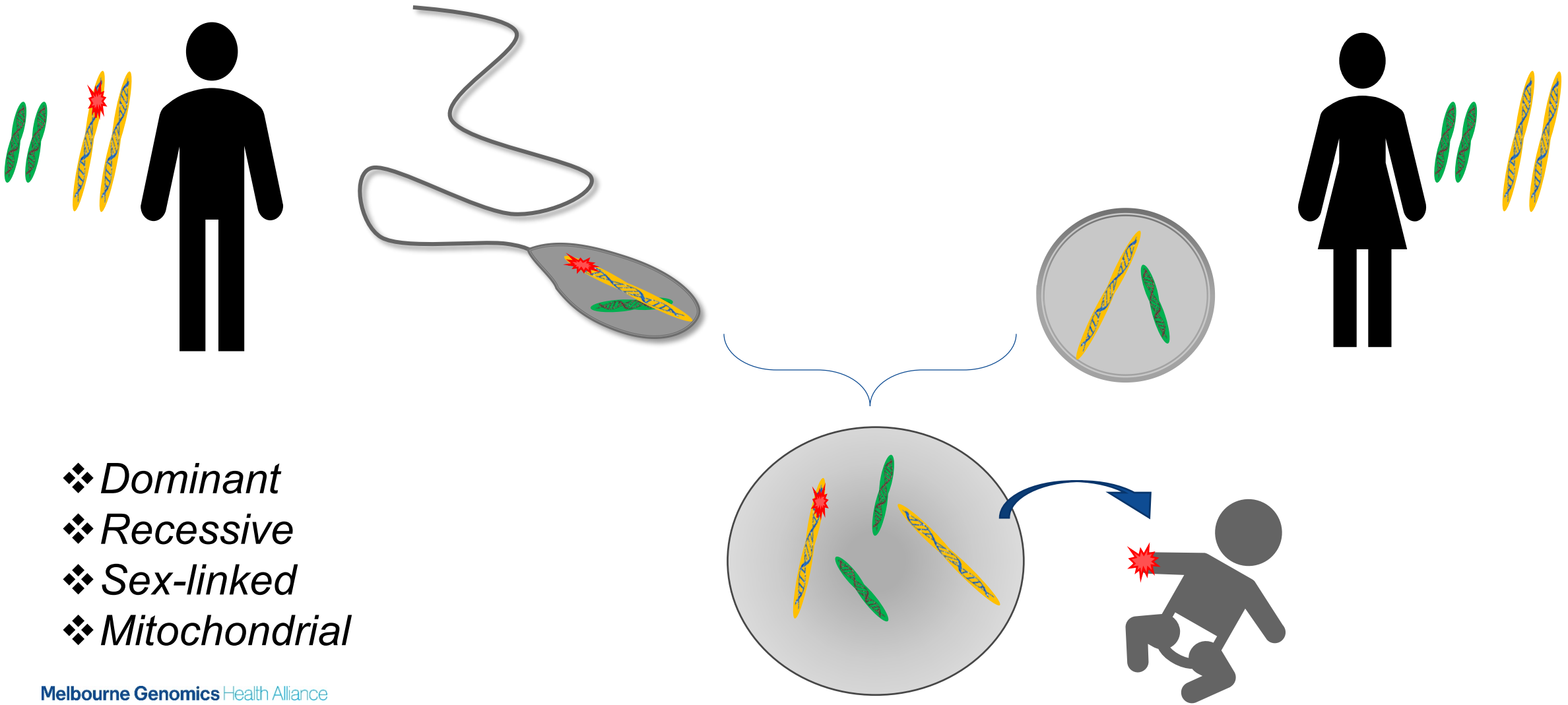
Inheriting the genome



Inheriting the genome

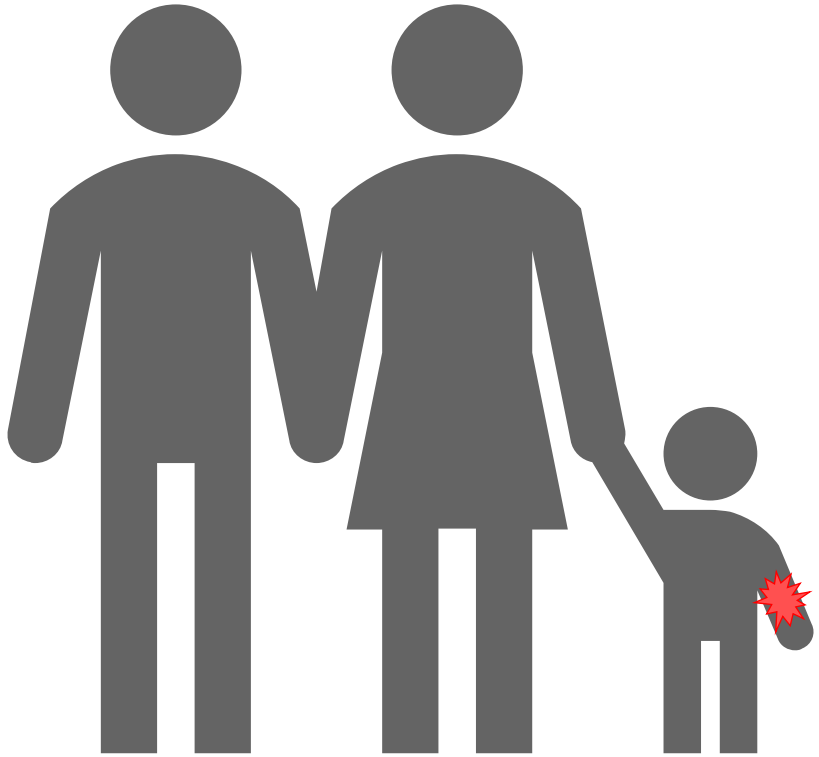


Inheritance patterns



- *Dominant*
- *Recessive*
- *Sex-linked*
- *Mitochondrial*

New variants – *de novo* variant



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Thank you