Outstanding care every time

NHS South East Genomic Medicine Service Alliance

NHS St George's University Hospitals NHS Foundation Trust

Applied Human Biology

Fundamentals of Genetics and Genomics in Nursing

Mark Mencias RN MSc
Neurogenetics Clinical Nurse Specialist
11th May 2023

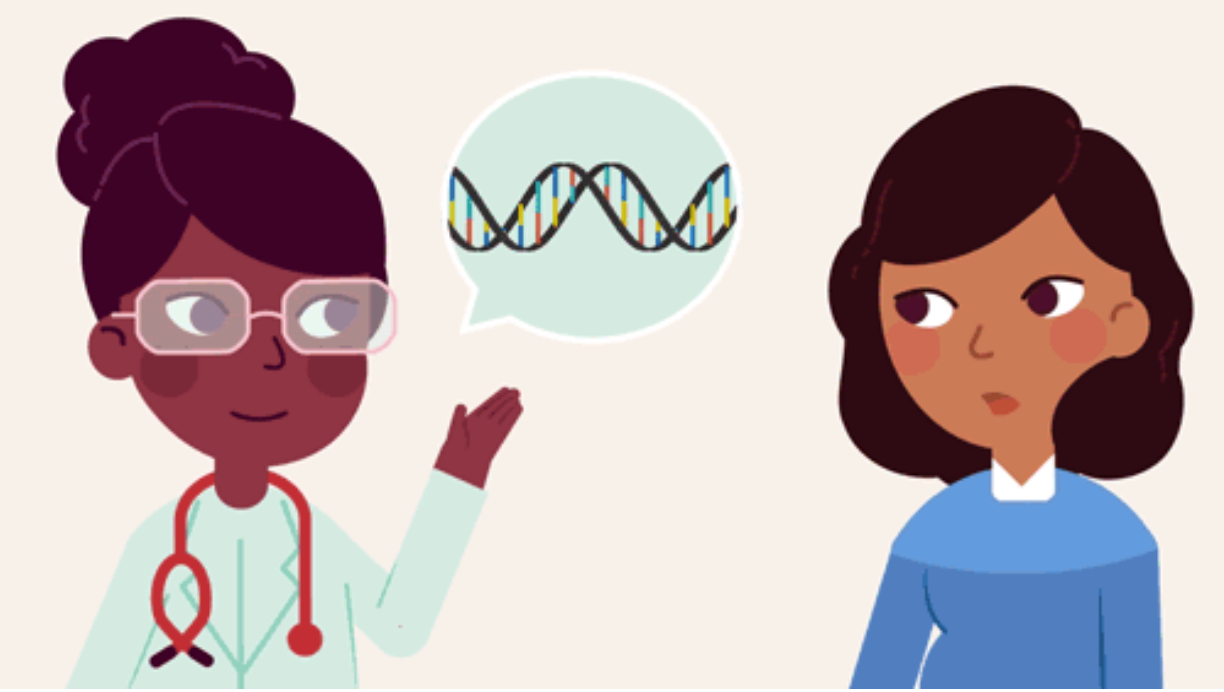
Introduction

Mark Mencias RN MSc
Neurogenetics Clinical Nurse Specialist

- Neurogenetics Clinical Nurse Specialist
- Nurse-Led Neurogenetics Clinic
- Base: Atkinson Morley Regional Neuroscience Centre
- South East Genomics Medicine Service Alliance
- Mainstream genomics in clinical neurology
  - Neuromuscular disorders
  - Genetic epilepsies
  - Movement disorders
  - Cognitive disorders
  - Paroxysmal CNS disorders
  - Mitochondrial disorders
- Researcher (particularly in rare & ultra rare diseases; drug development; bioinformatics)
- Workforce upskilling & higher education.

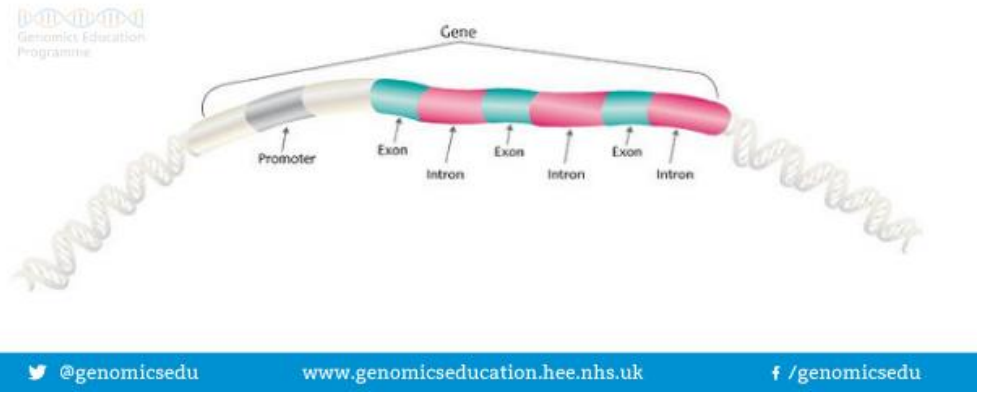
Learning Outcomes

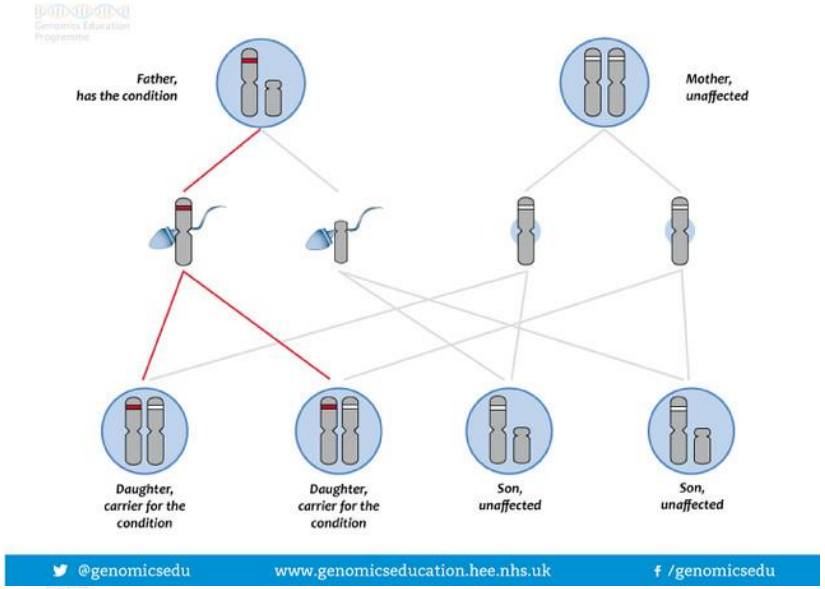
- Gain an understanding of the basics of genetics and genomics
- Explore the impact of genetics and genomics in providing healthcare.
- The role of nurses in the genomic medicine era.

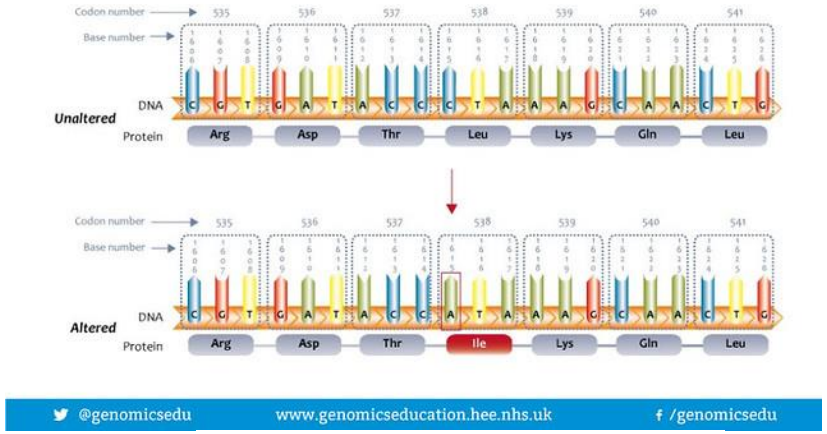


Genetics

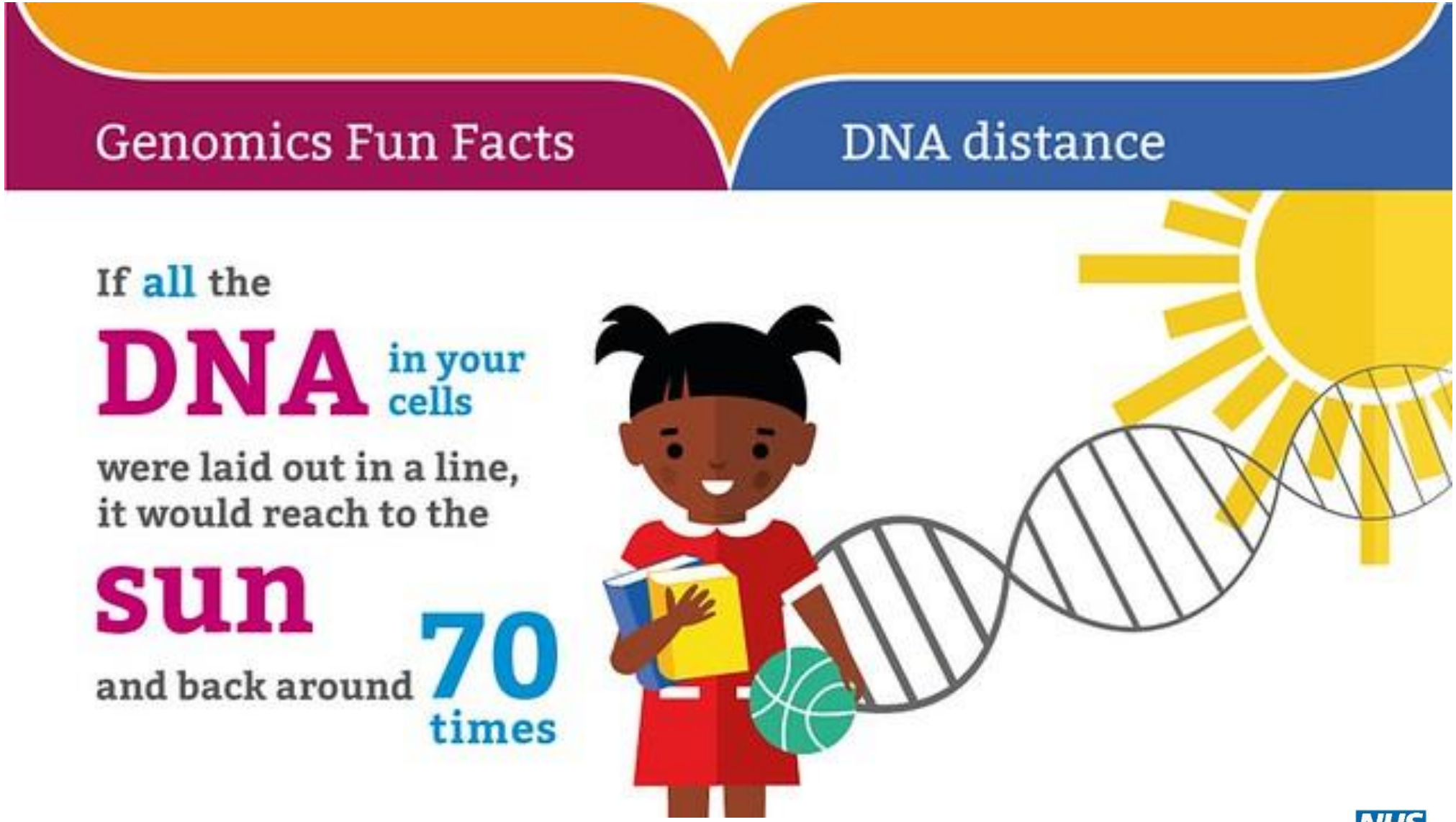
- **Genes:** function & composition
- **Heredity:** inheritance
- **Variation:** Difference in DNA sequences between individuals





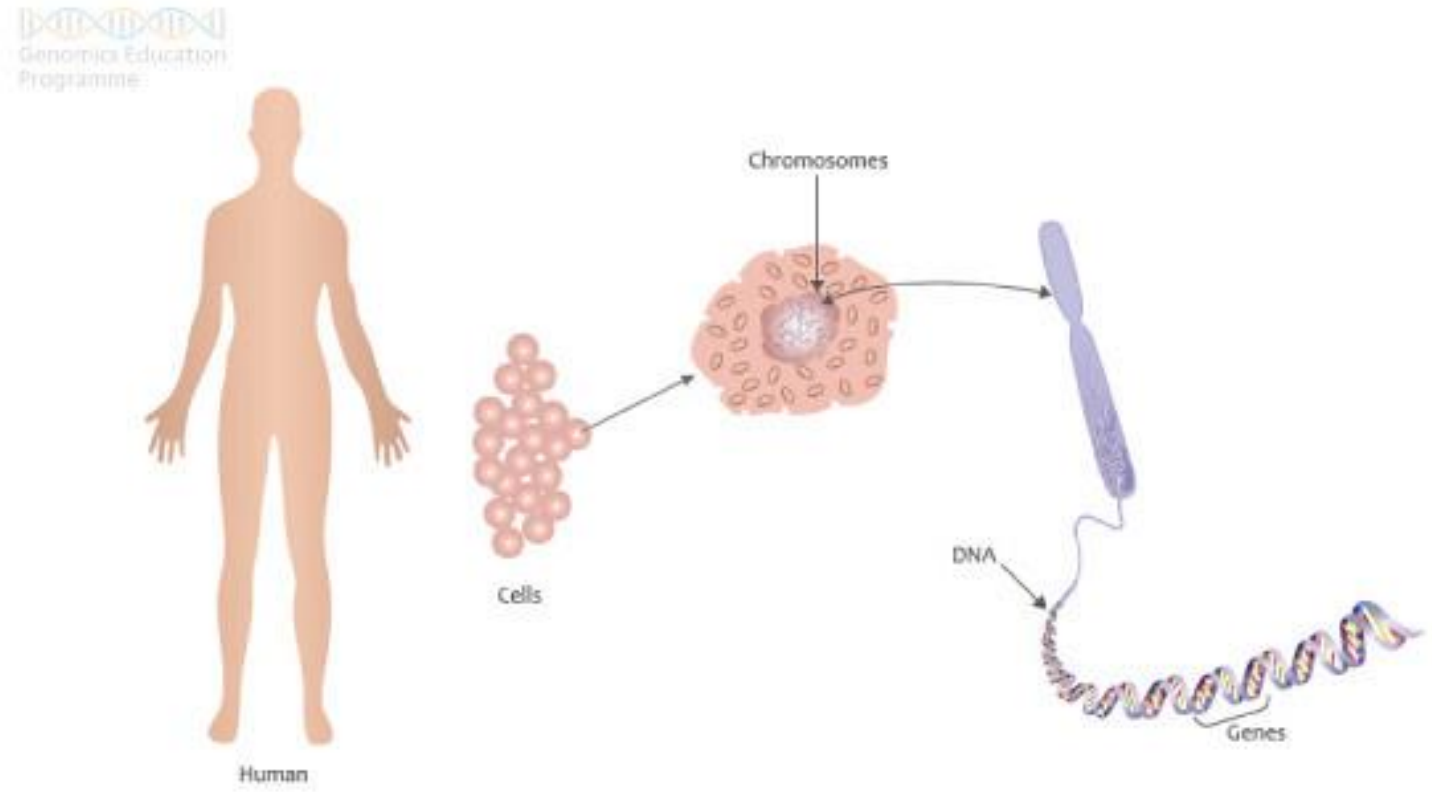


Genetics


Genomics Fun Facts
DNA distance
If all the
DNA in your cells
were laid out in a line,
it would reach to the
sun
and back around 70 times

Genomics

- Complete set of genetic information
- 20000 to 25000 genes



Genomics

Genomics Fun Facts

Your genome is only around

0.1%

different from any other person's,

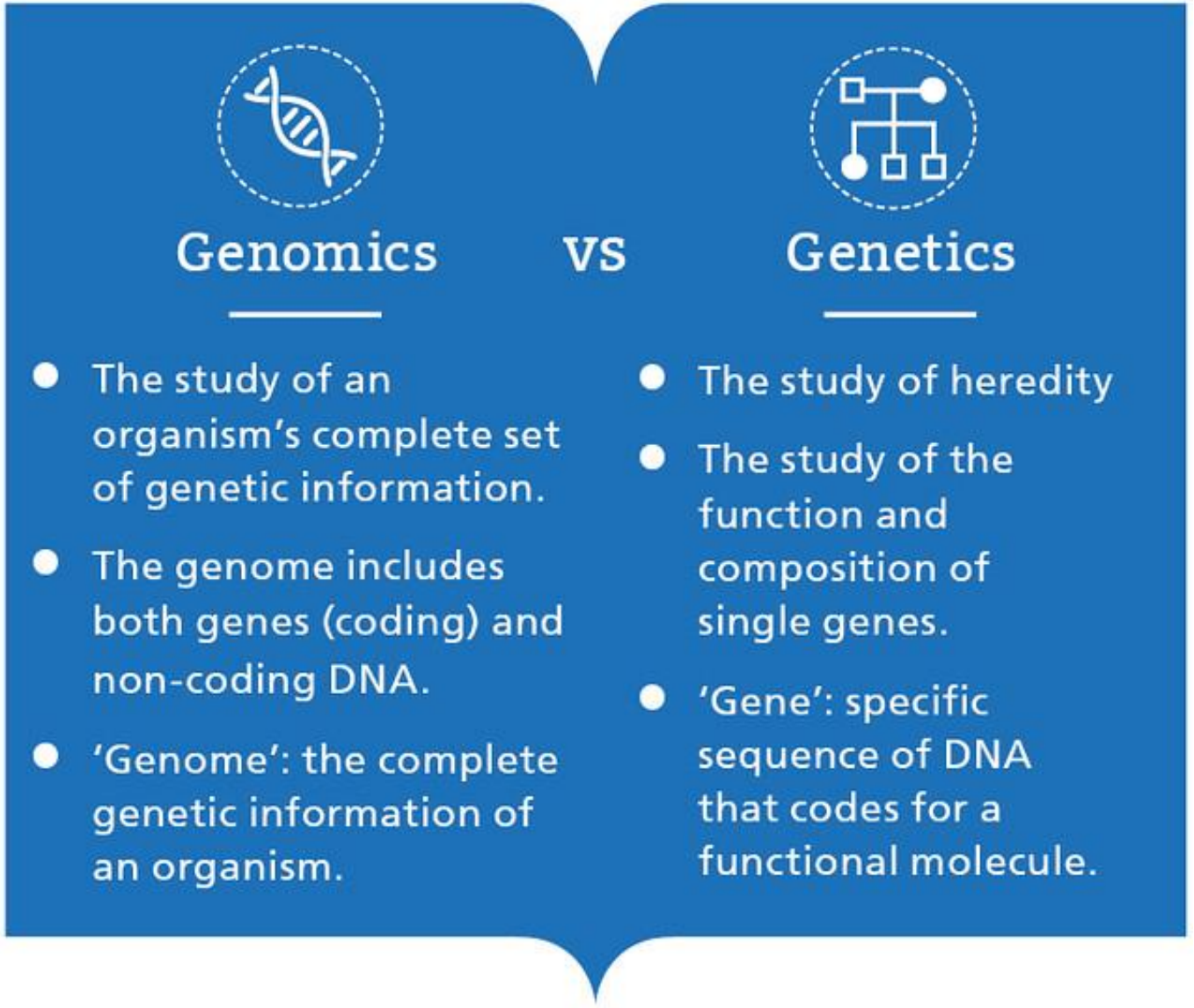
but that equates to

3 million

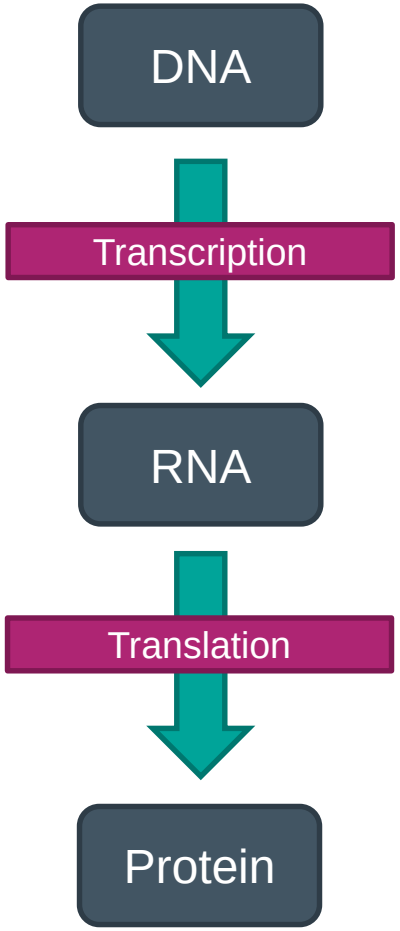
differences in your DNA

Genetic differences

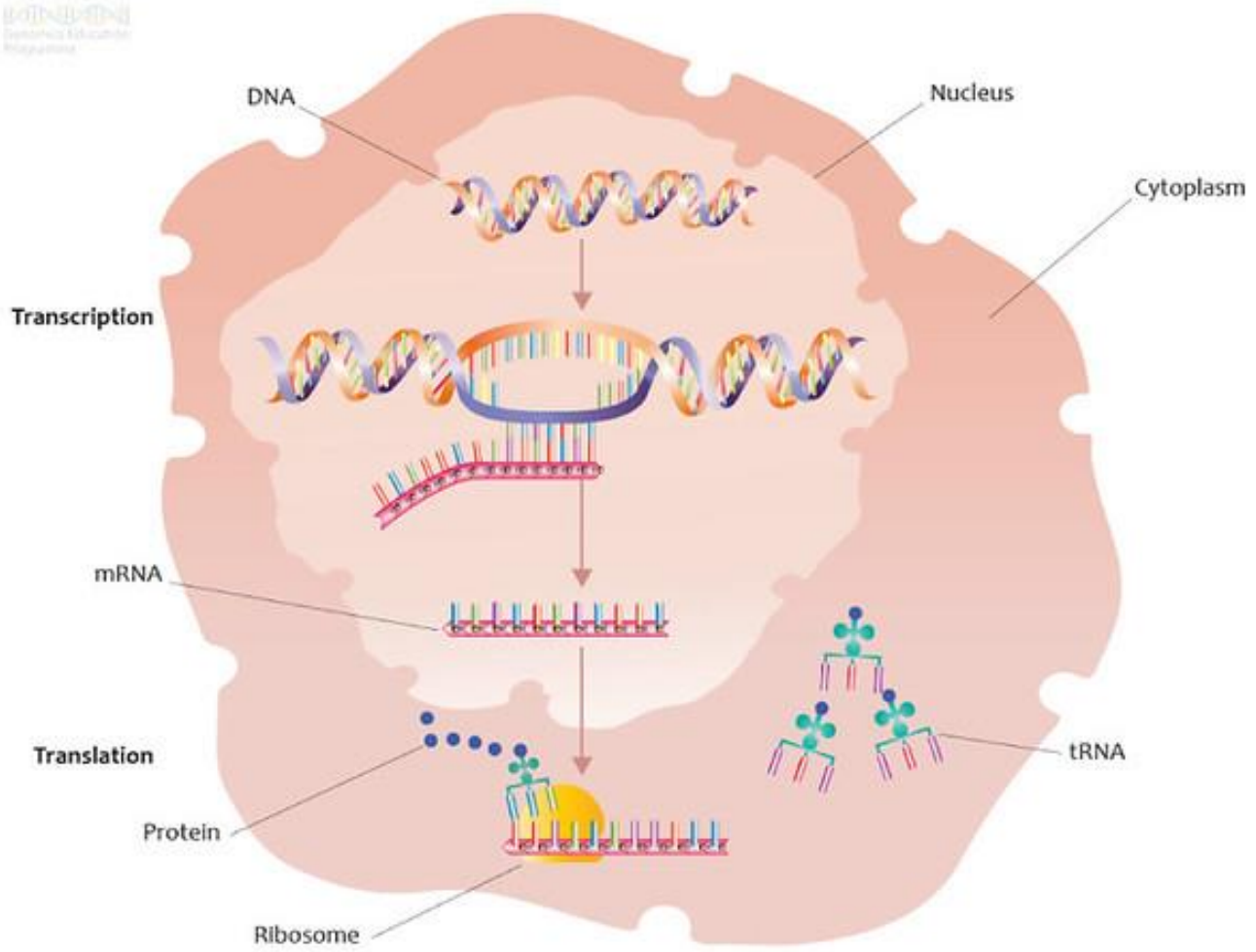
Genetics vs Genomics



Central Dogma of Biology

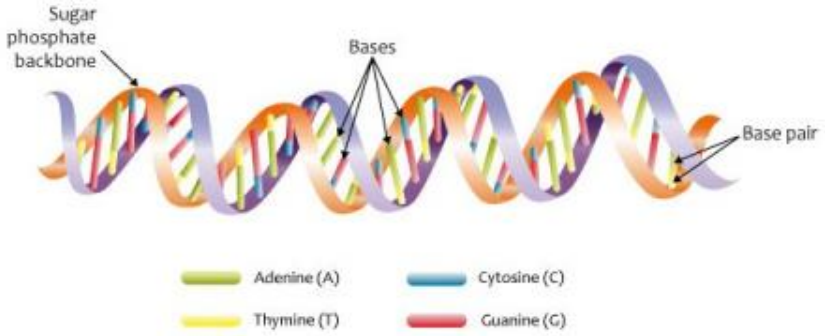


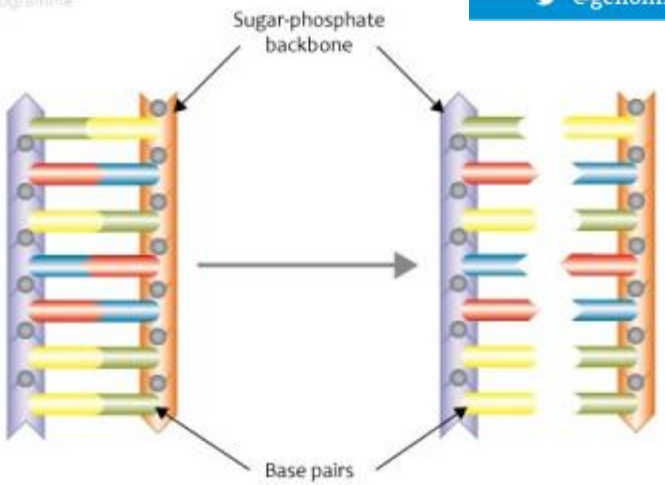
From DNA to RNA to Amino Acid



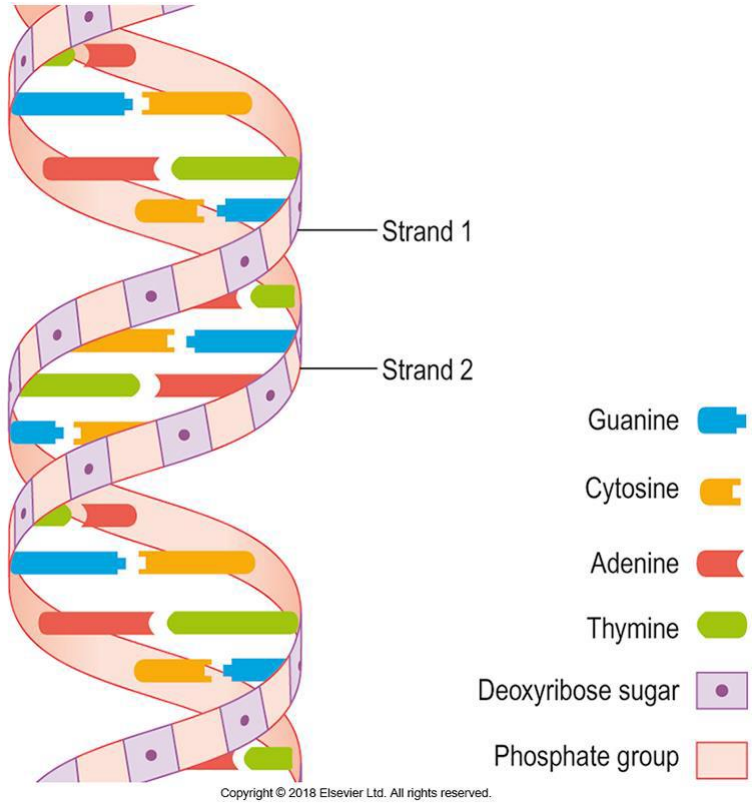
Deoxyribonucleic acid (DNA)

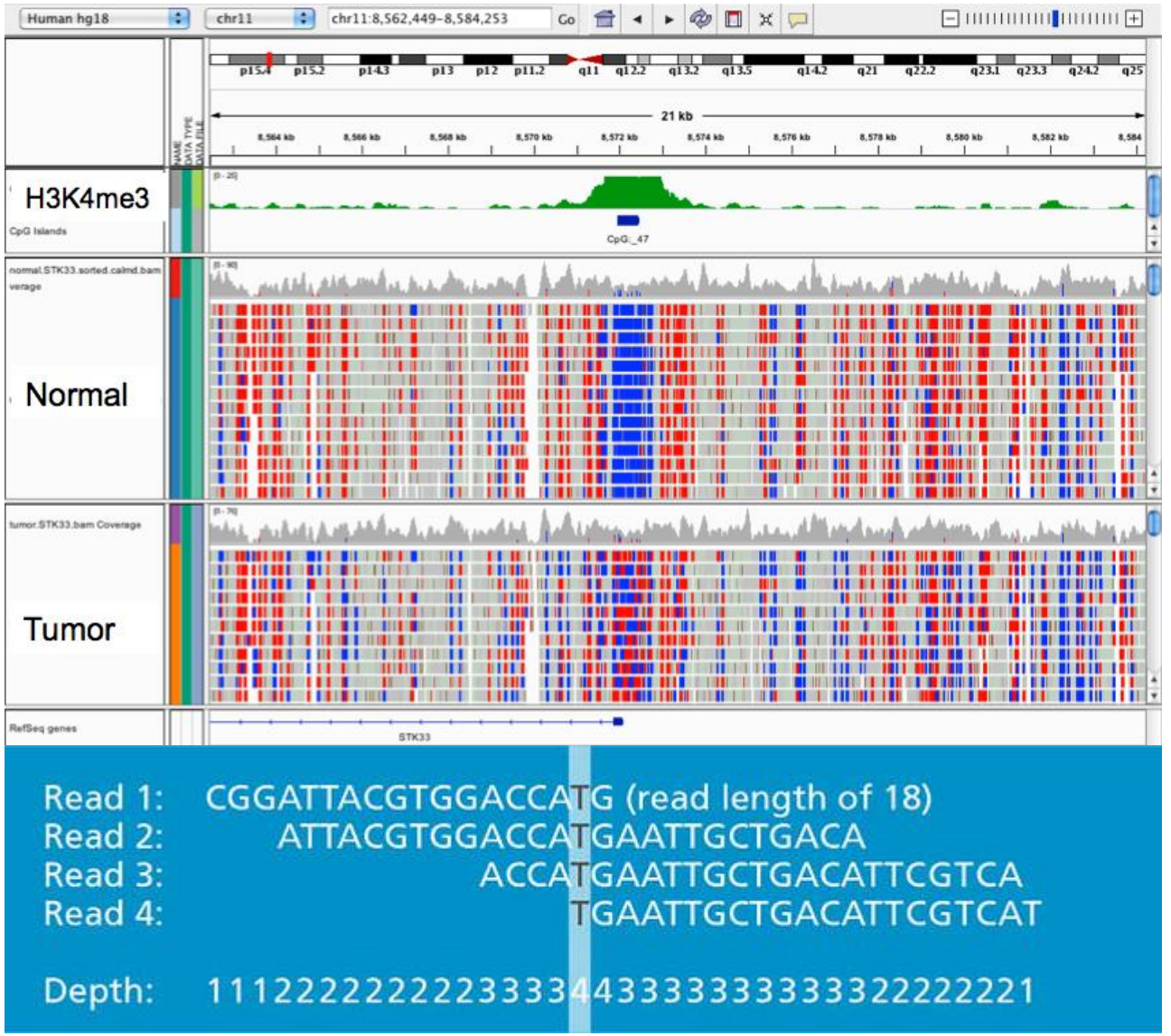
- Double stranded
- Nucleotides
- Double helix
- Sugar & phosphate groups



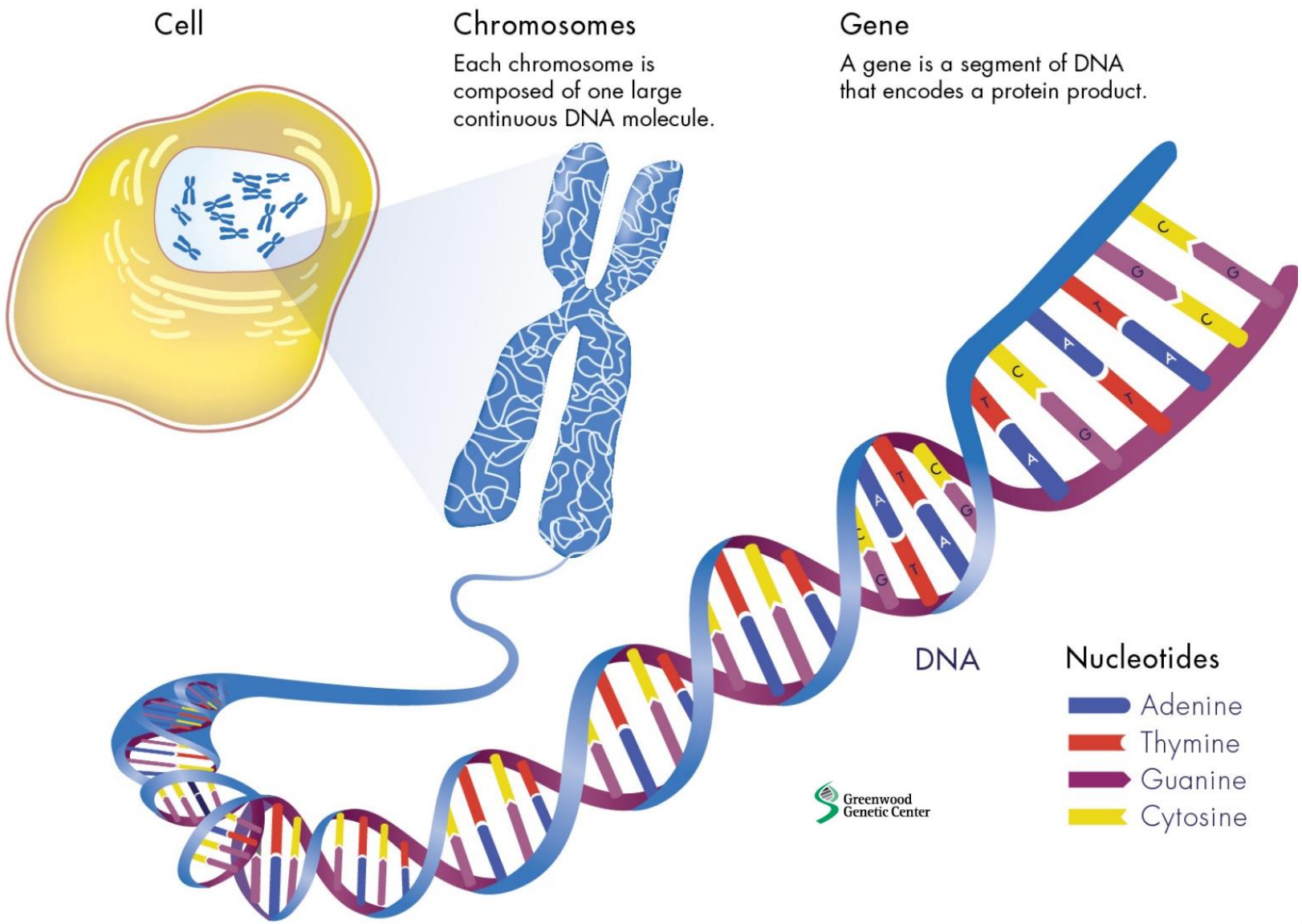


Genetic Code





Chromosomes



Chromosome Staining & Karyotyping

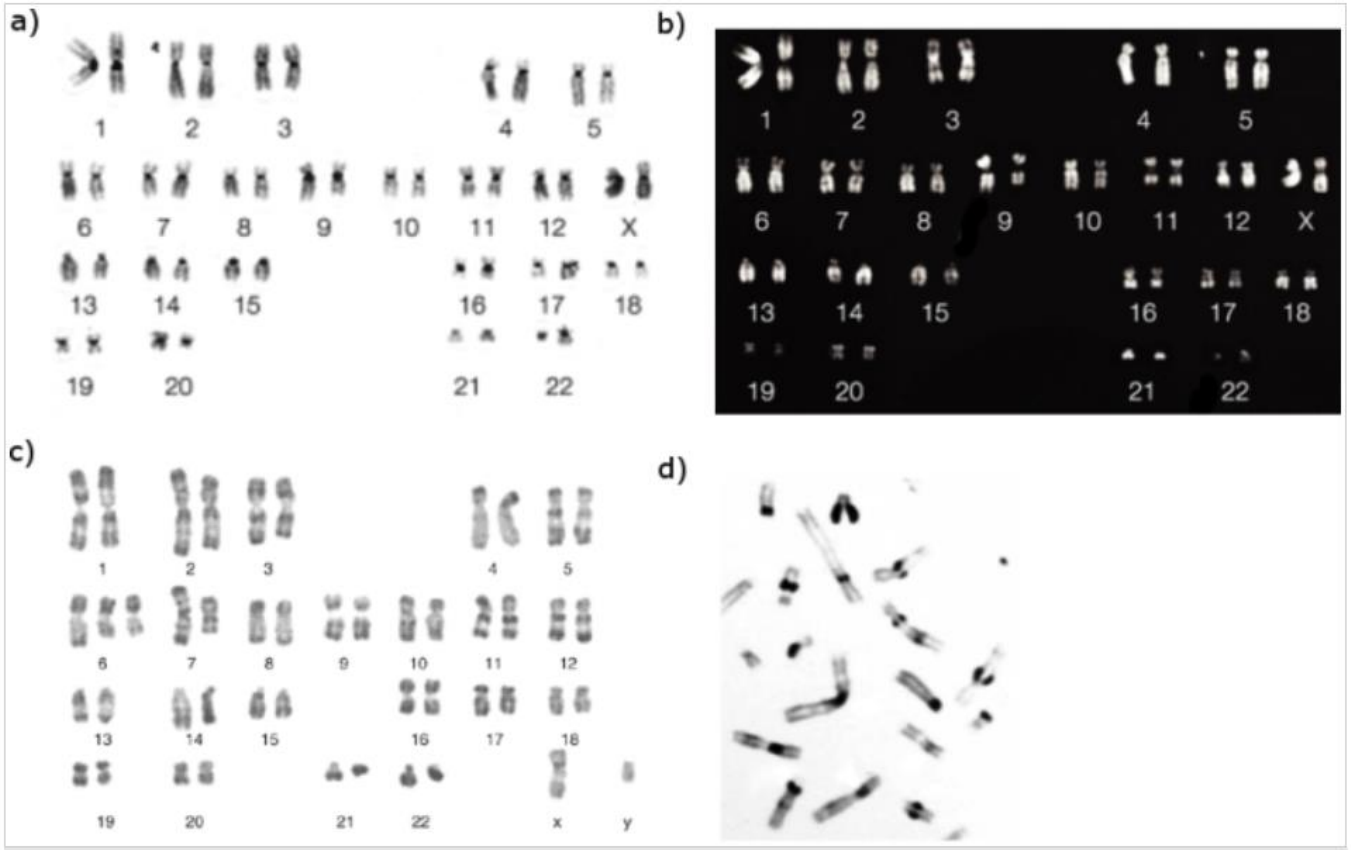
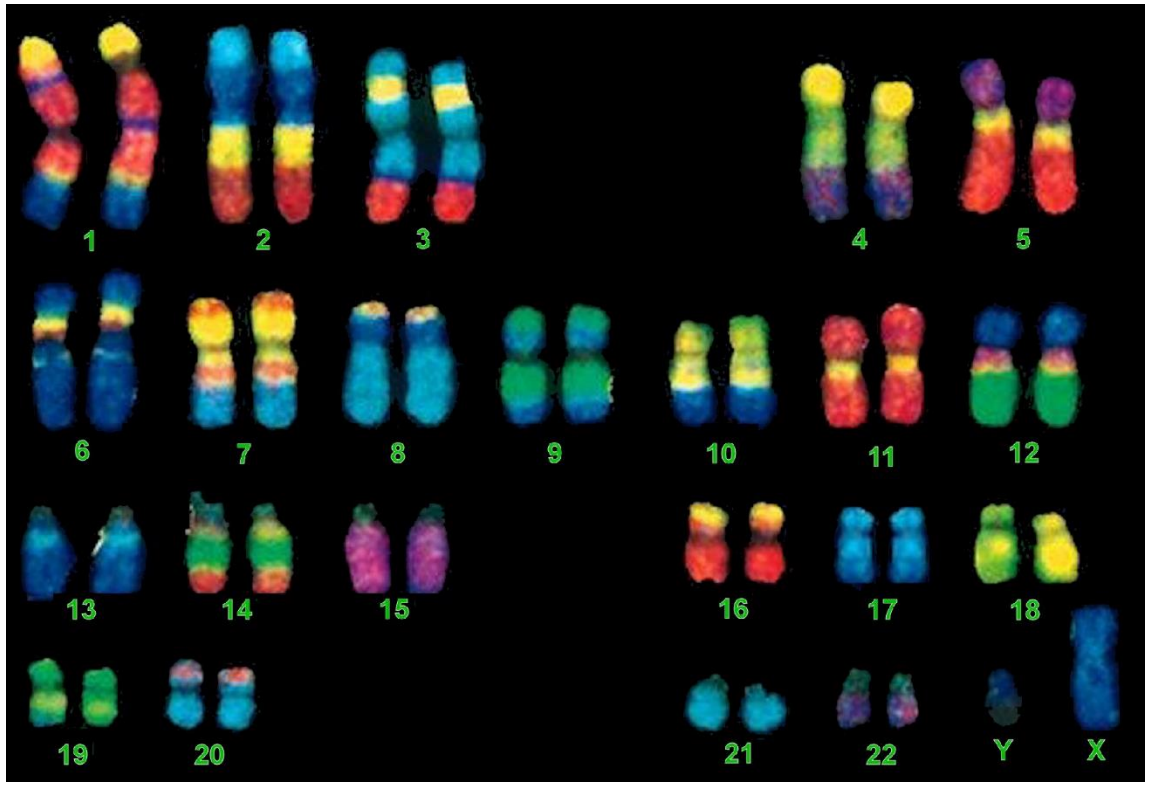


Figure 1: Chromosome banding revealed by different staining techniques.
Different chromosomal staining techniques reveal variations in chromosome structure. Cytogeneticists use these patterns to recognize the differences between chromosomes and enable them to link different disease phenotypes to chromosomal abnormalities. Giemsa banding (a), Q-banding (b), R-banding (c) and C-banding (d) are shown.



Sex Chromosomes

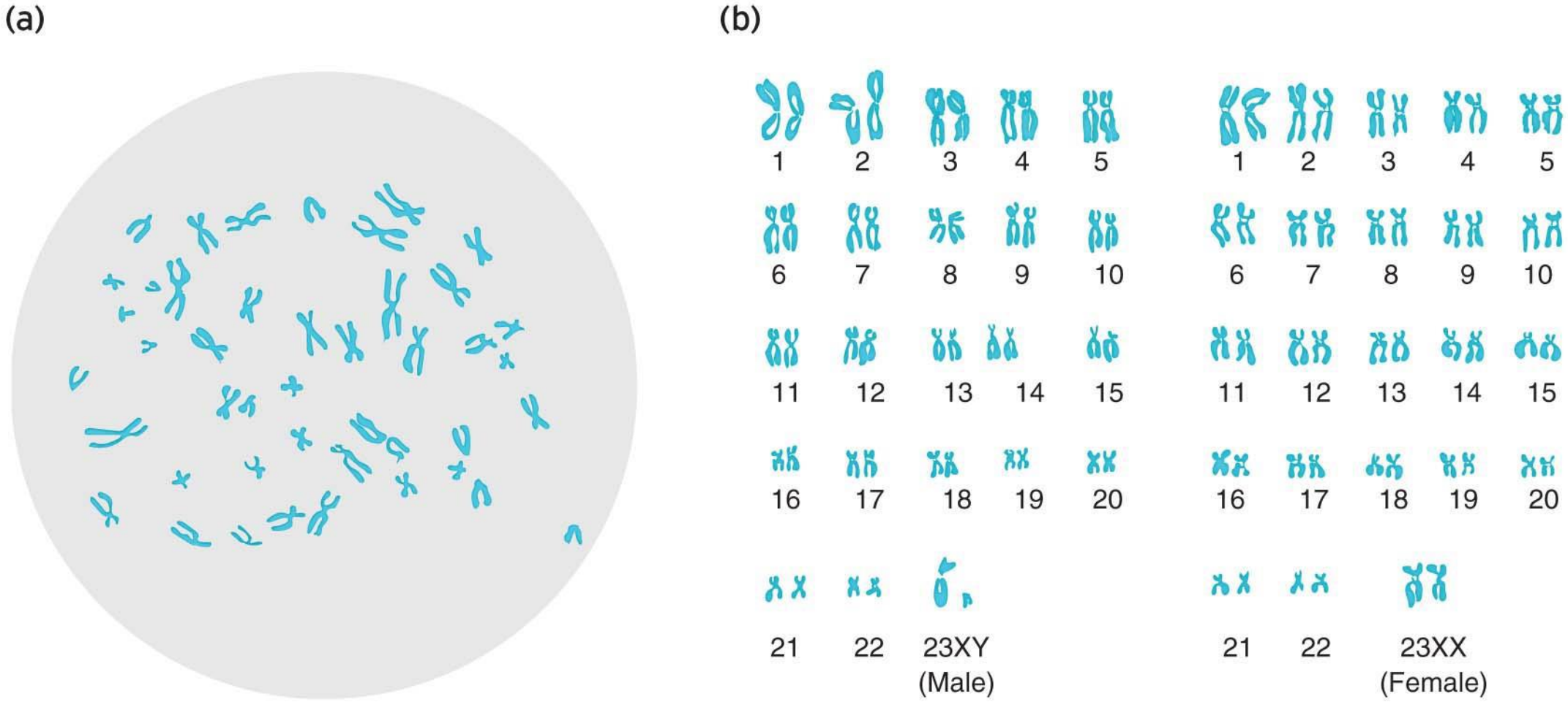
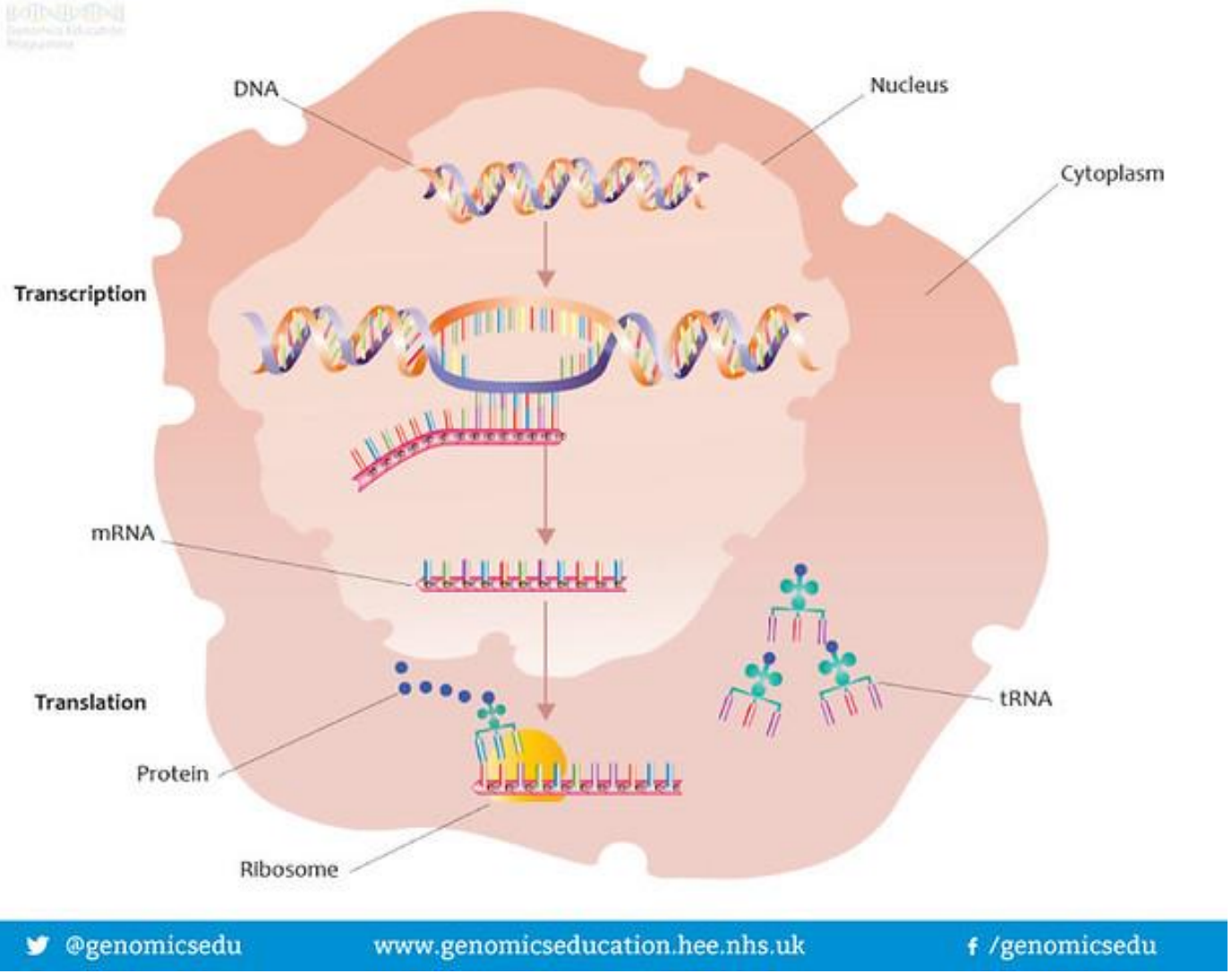
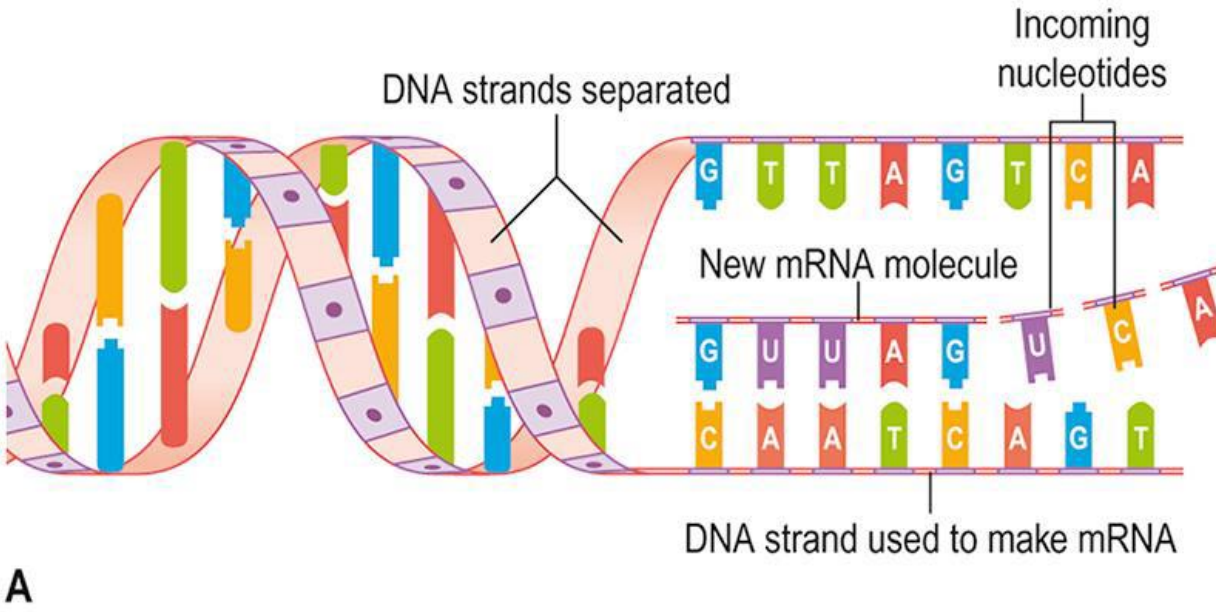


Figure 2.2 The human chromosome (a) Chromosome smear (b) Human karyotype

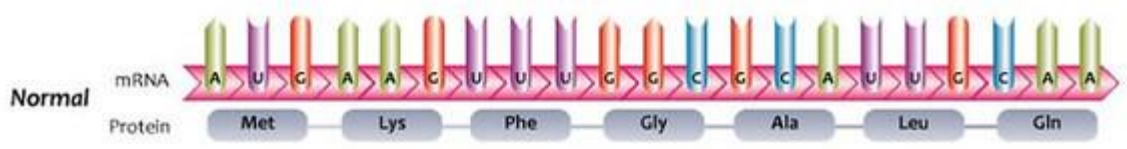
Protein Synthesis



Messenger Ribonucleic Acid (mRNA)

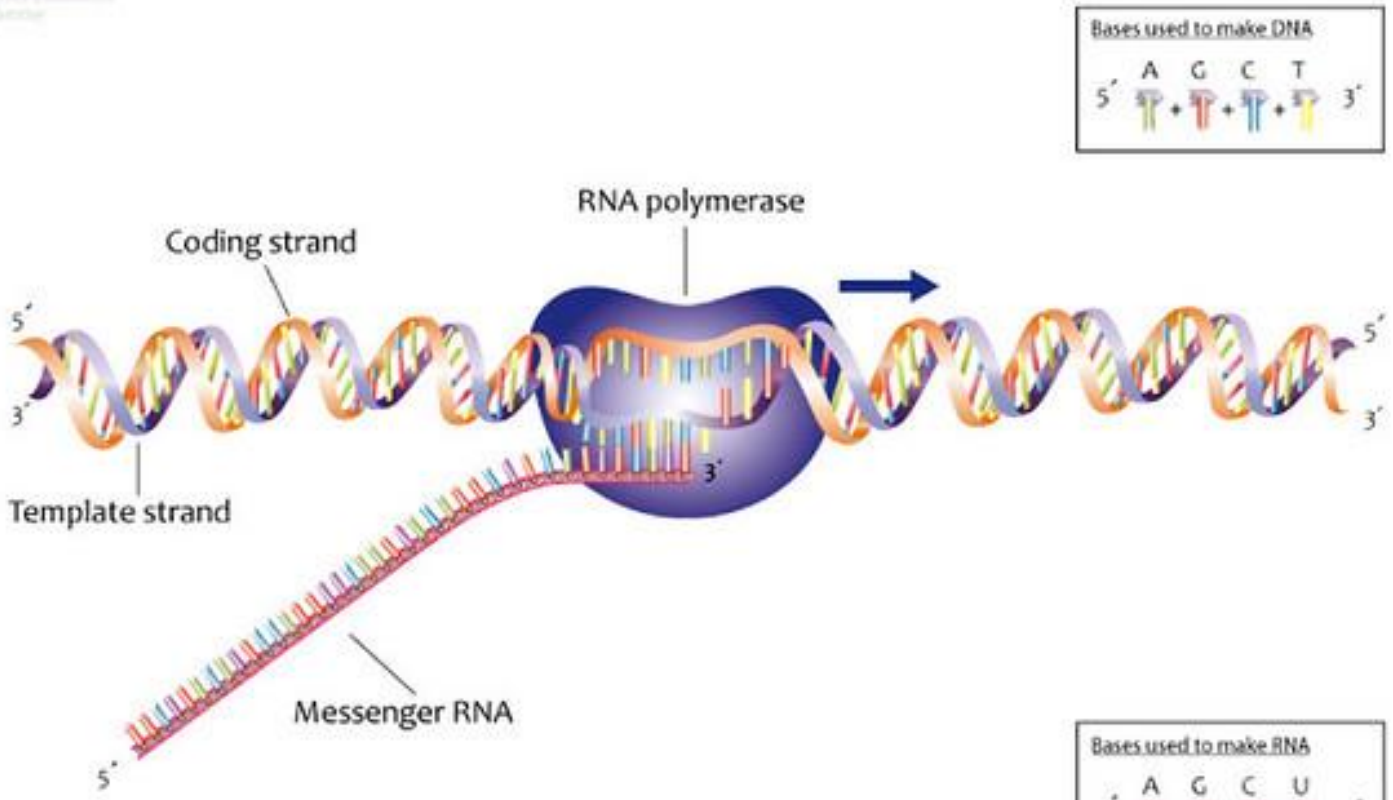


A

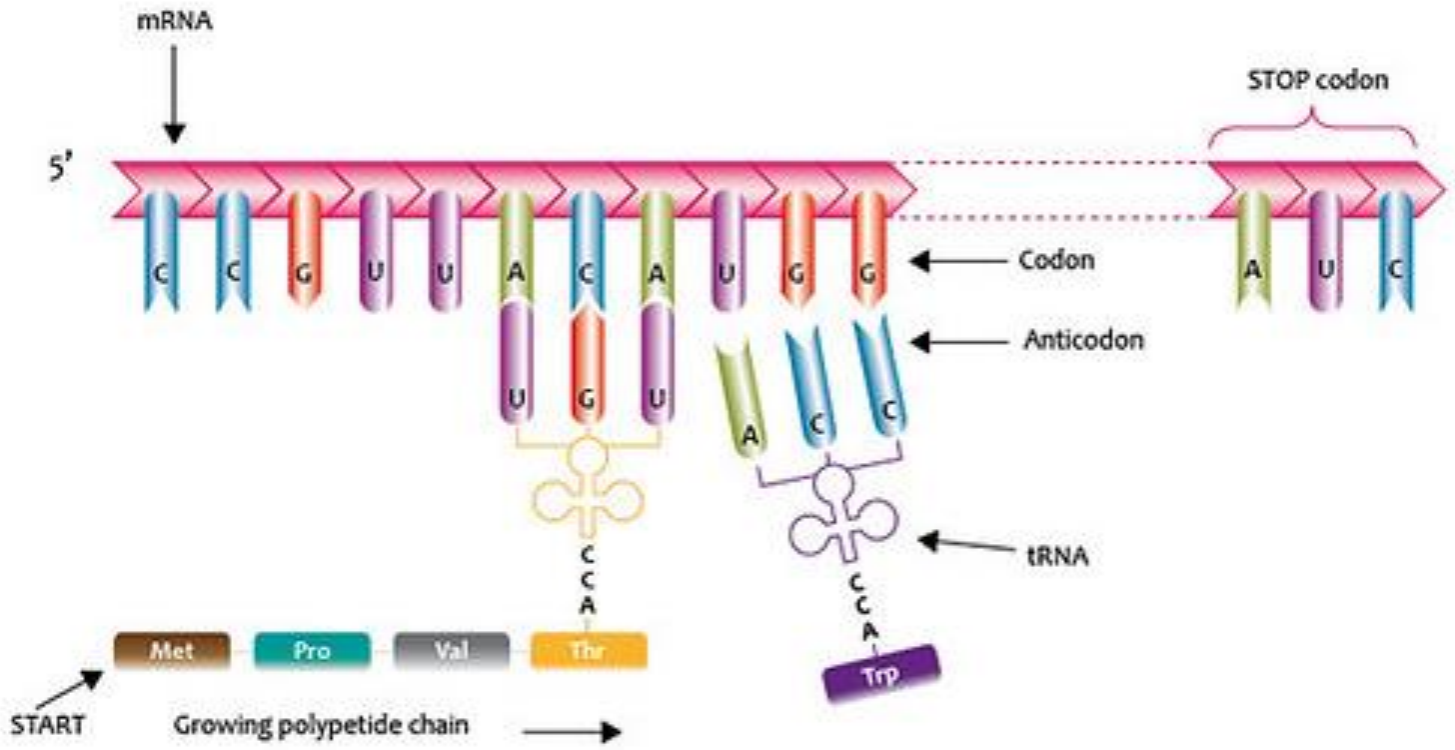


Adapted from Campbell NA (ed). Biology, 2nd ed, 1990

Transcription



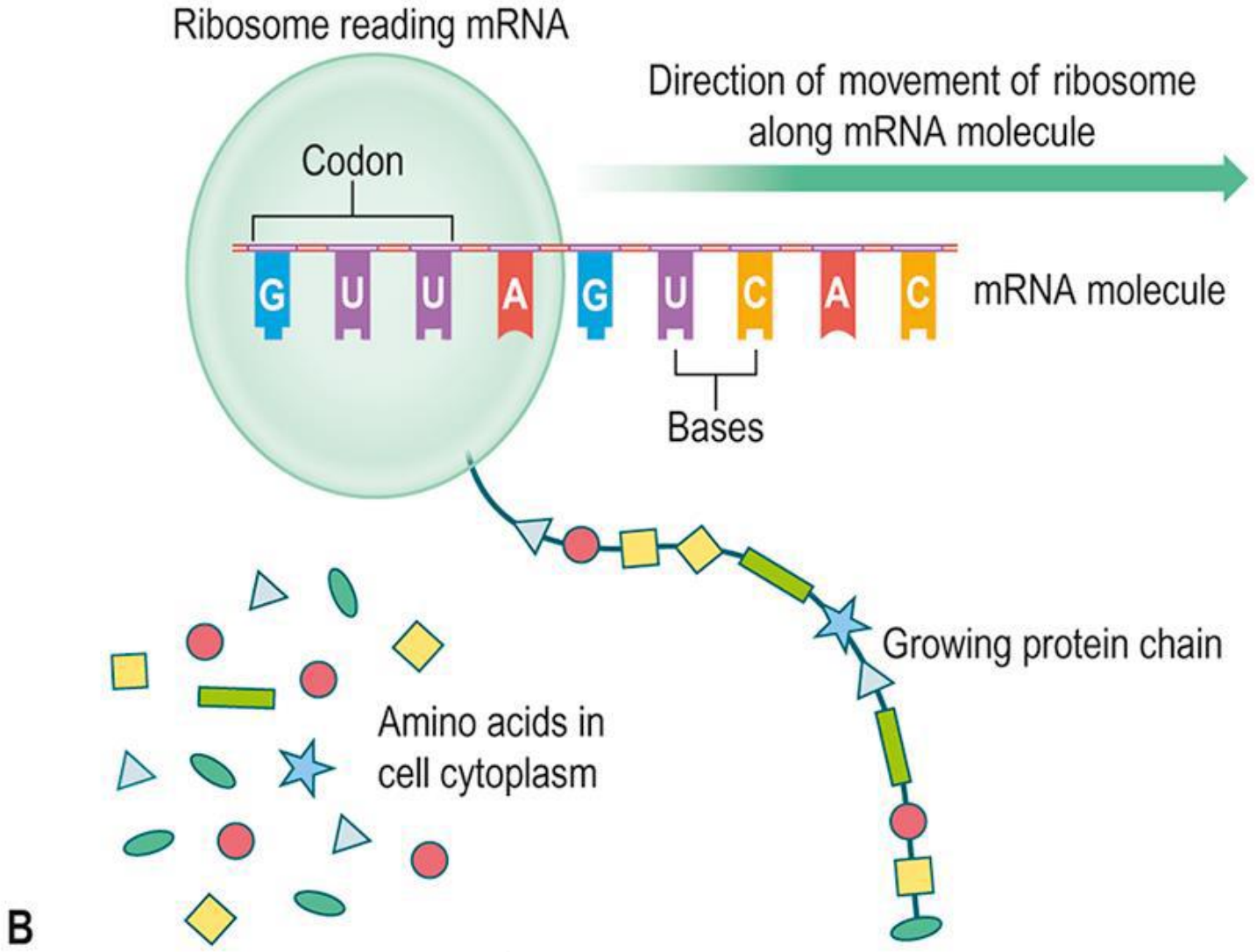
Translation



Second letter

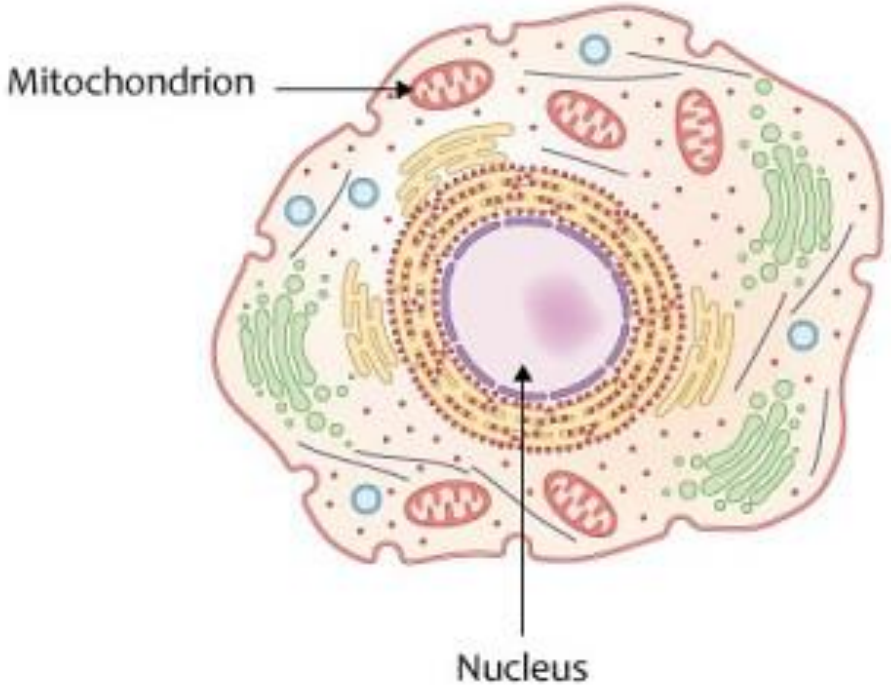
First letter	U	C	A	G	Third letter
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC **UAA Stop** **UAG Stop**	UGU Cys UGC **UGA Stop** UGG Trp	U C A G
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg	U C A G
A	AUU AUC AUA Ile **AUG Met**	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU GUC GUA GUG Val	GCU GCC GCA GCG Ala	GAU Asp GAC GAA Glu GAG	GGU GGC GGA GGG Gly	U C A G

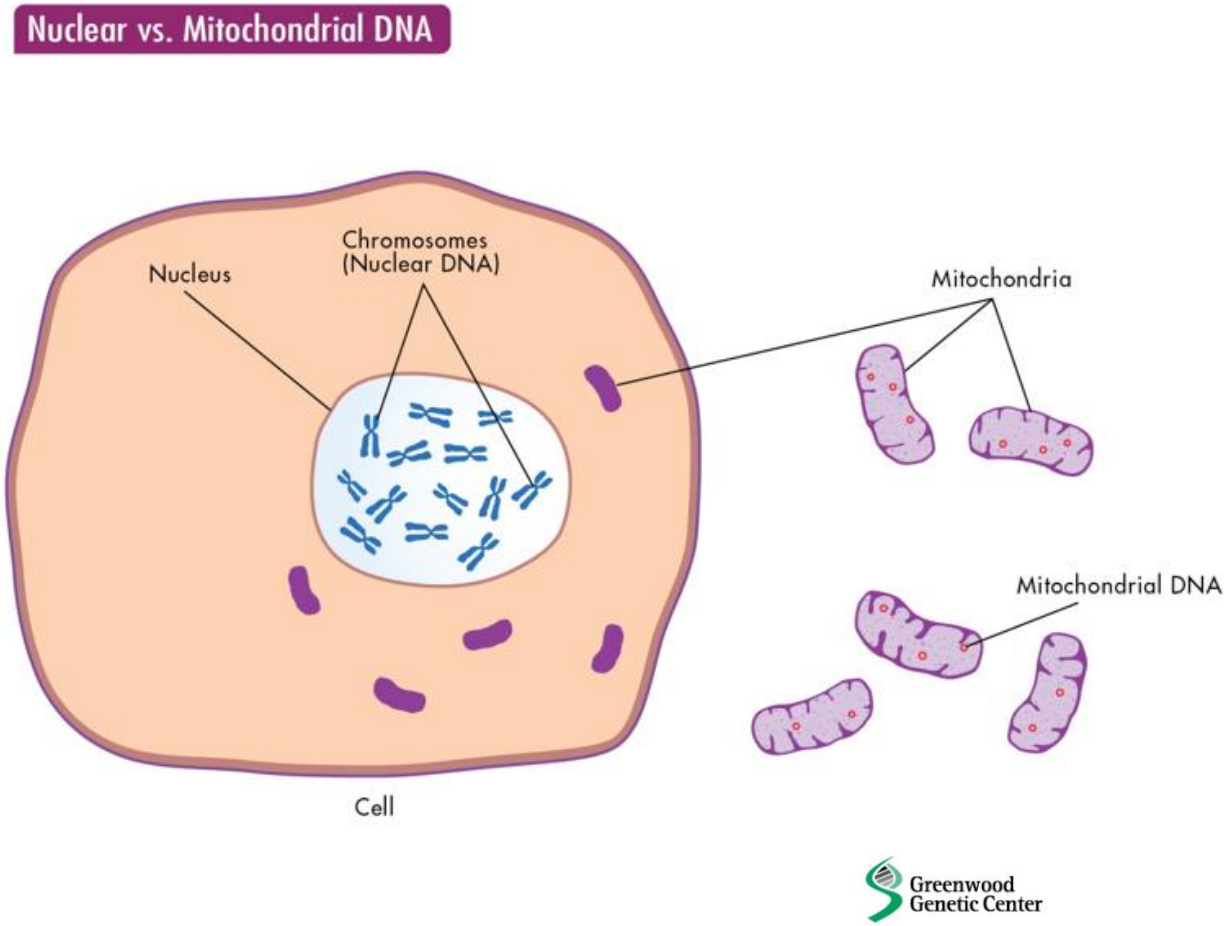
Translation



From DNA to Protein

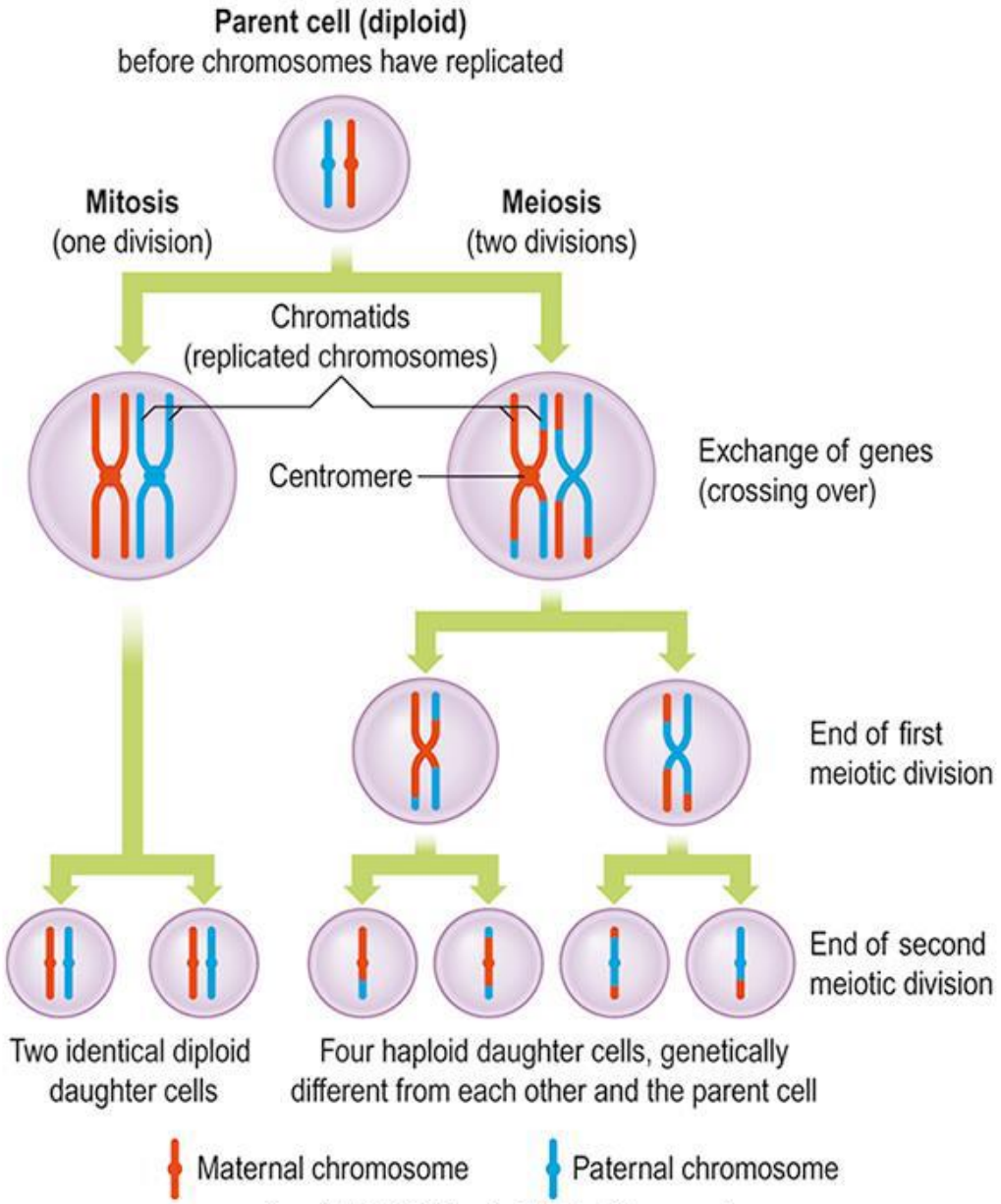
Mitochondrial DNA



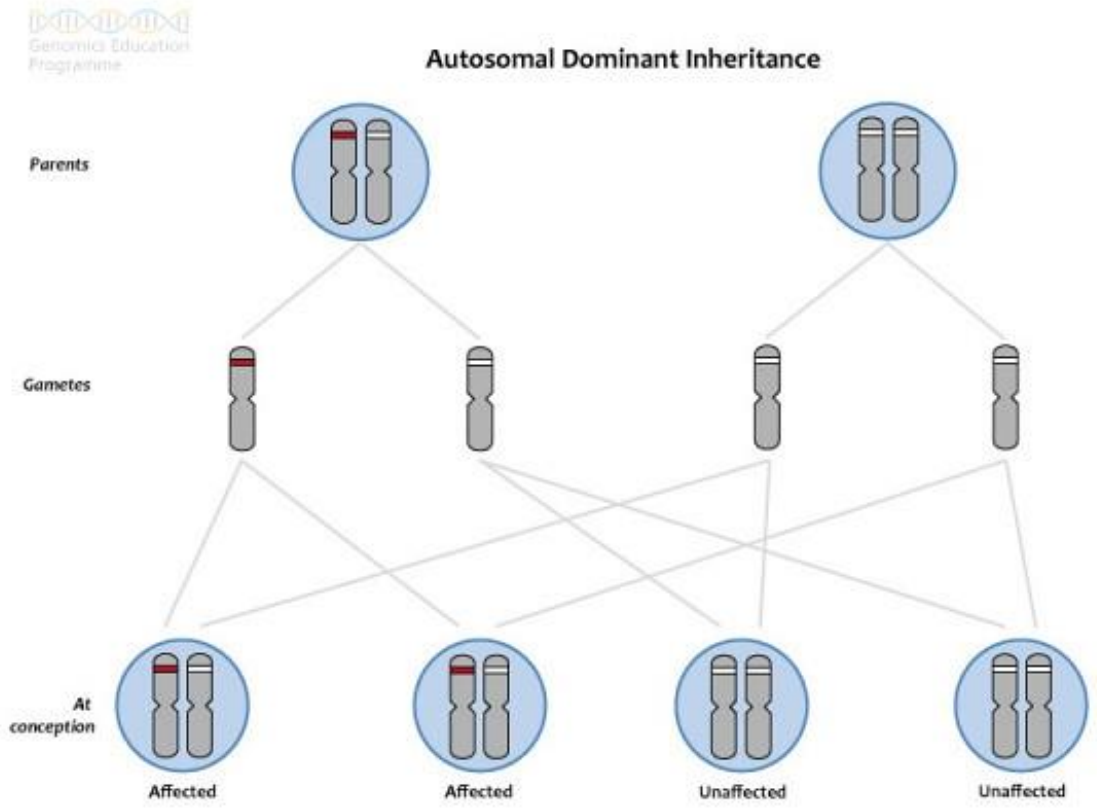


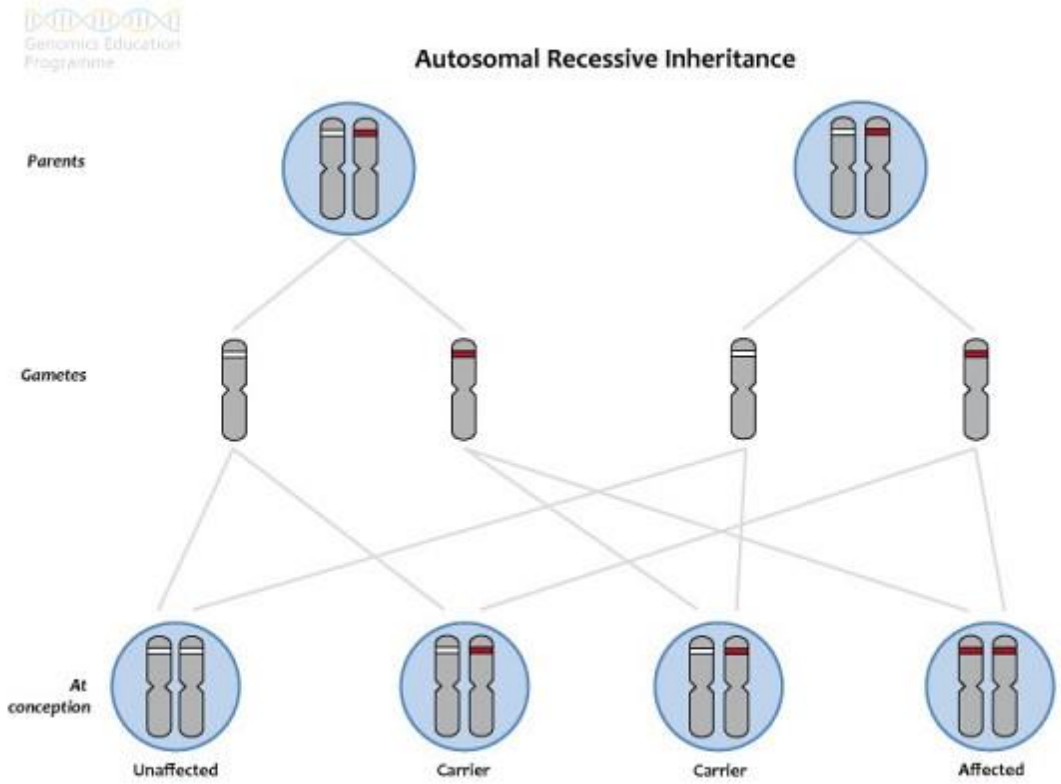
Greenwood Genetic Center

Cell Division

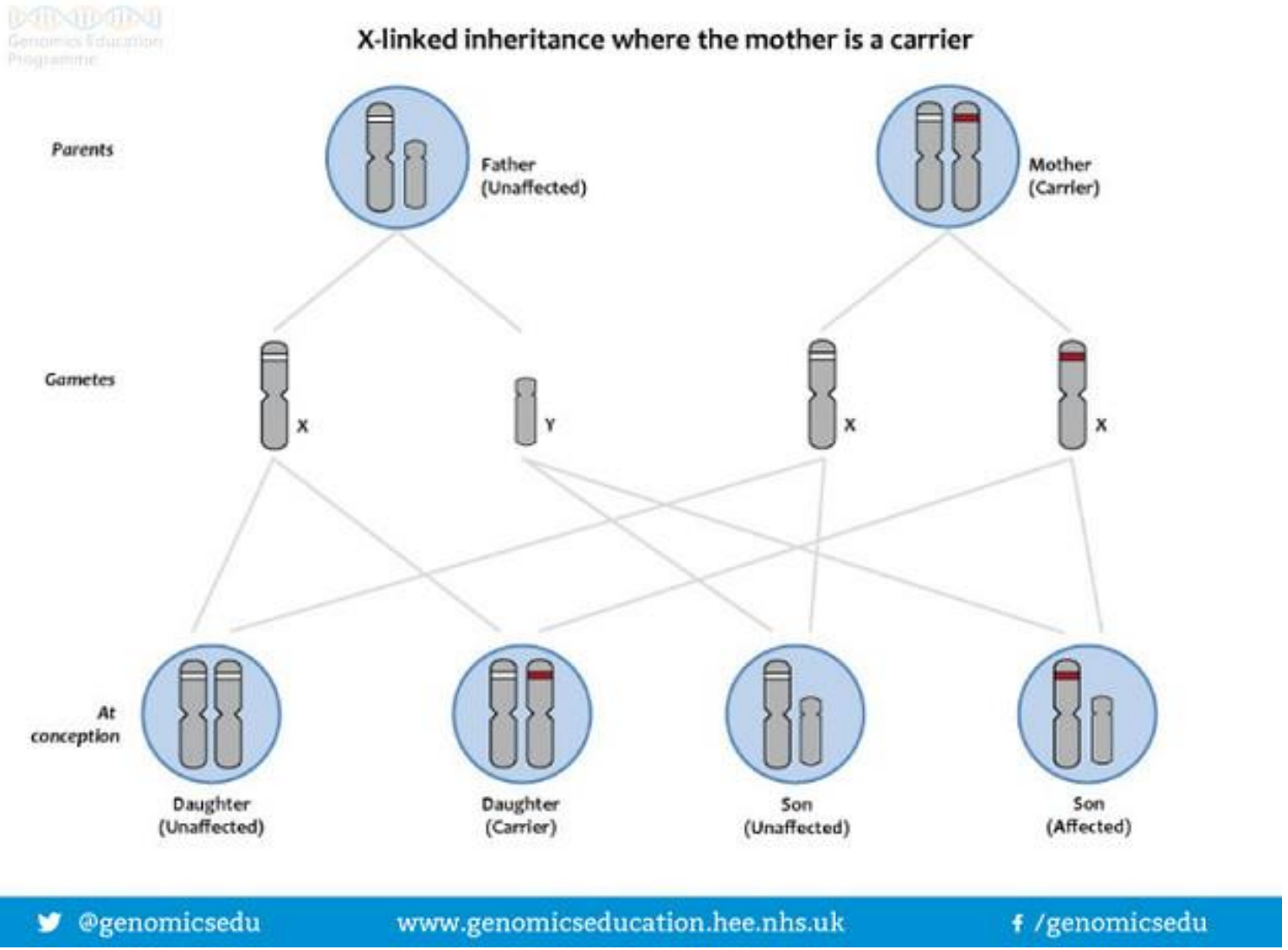


Genetic Basis of Inheritance





Sex-Linked Inheritance



Case Study

- History of presenting illness:
  - 2 y/o male presenting with abnormal body movement for 3 days.
  - On/off fever for 2 days; up rolled eyes with vacant stare, open mouth, drooling of saliva; stiffening and abnormal movement of right upper & lower limb; lip smacking; urinary incontinence.
  - First seizure at 2 months of age. Observed seizure lasted for more than 10 minutes. Used to have up to 24 seizures per day. Was on Levetiracetam.
- Family & social Hx:
  - Patient is 2nd child of non-consanguineous parents; term but delivered via CS due to fetal distress. Did not cry at birth. Birthweight and head circumference were normal at the time. Normal milestones until 18 months of age.
  - 1st child – fit and well
  - Mother – Hx of hydatidiform mole; had 3 successive spontaneous abortions after 1st child.

Case Study

- Clinical examination
  - V/S: PR - 142 bpm; RR - 28 bpm; BP - 100/70 mmHg; T – 37.9 C; SpO2 99%
  - Pallor
  - Global developmental delay; no head control; neg finger grasp or reaching for objects; delayed motor movements
  - Head circumference 46.5 cm; weight - 10kg; height – 83cm
  - Alternating hemiclonic, generalised tonic-clonic seizure & status epilepticus which later followed by absence seizures.

Case Study

- Lab – normal
- EEG – no significant findings
- MRI – prominent extra-axial CSF spaces with proportionate dilatation of the ventricles consistent with global cerebral atrophy

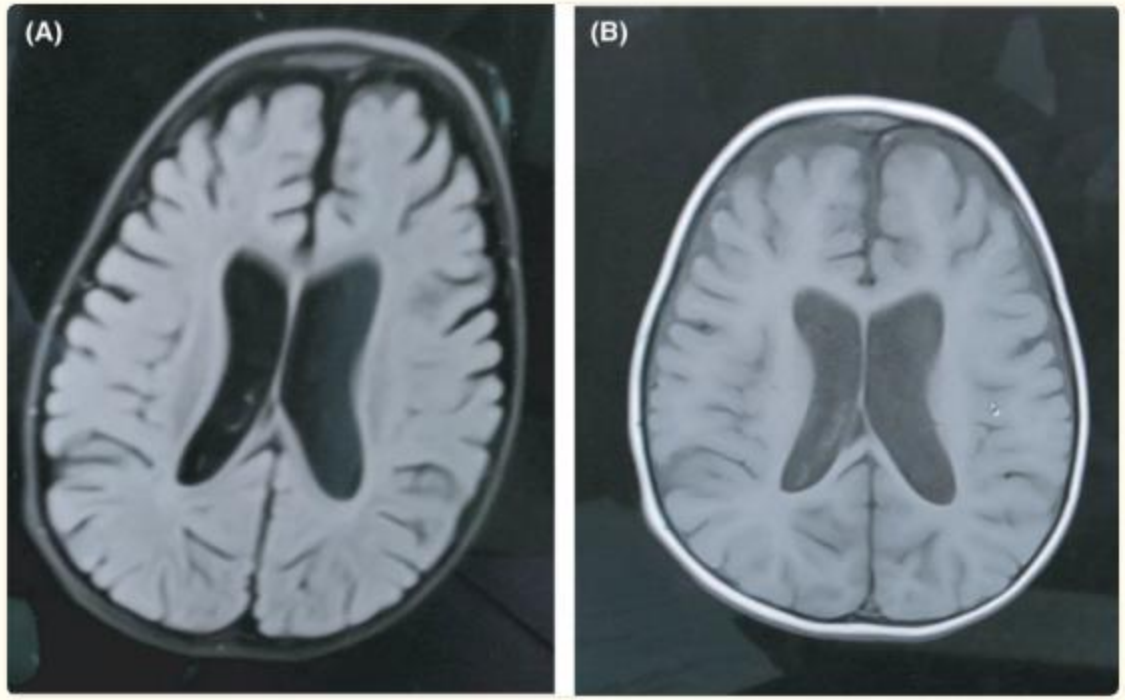
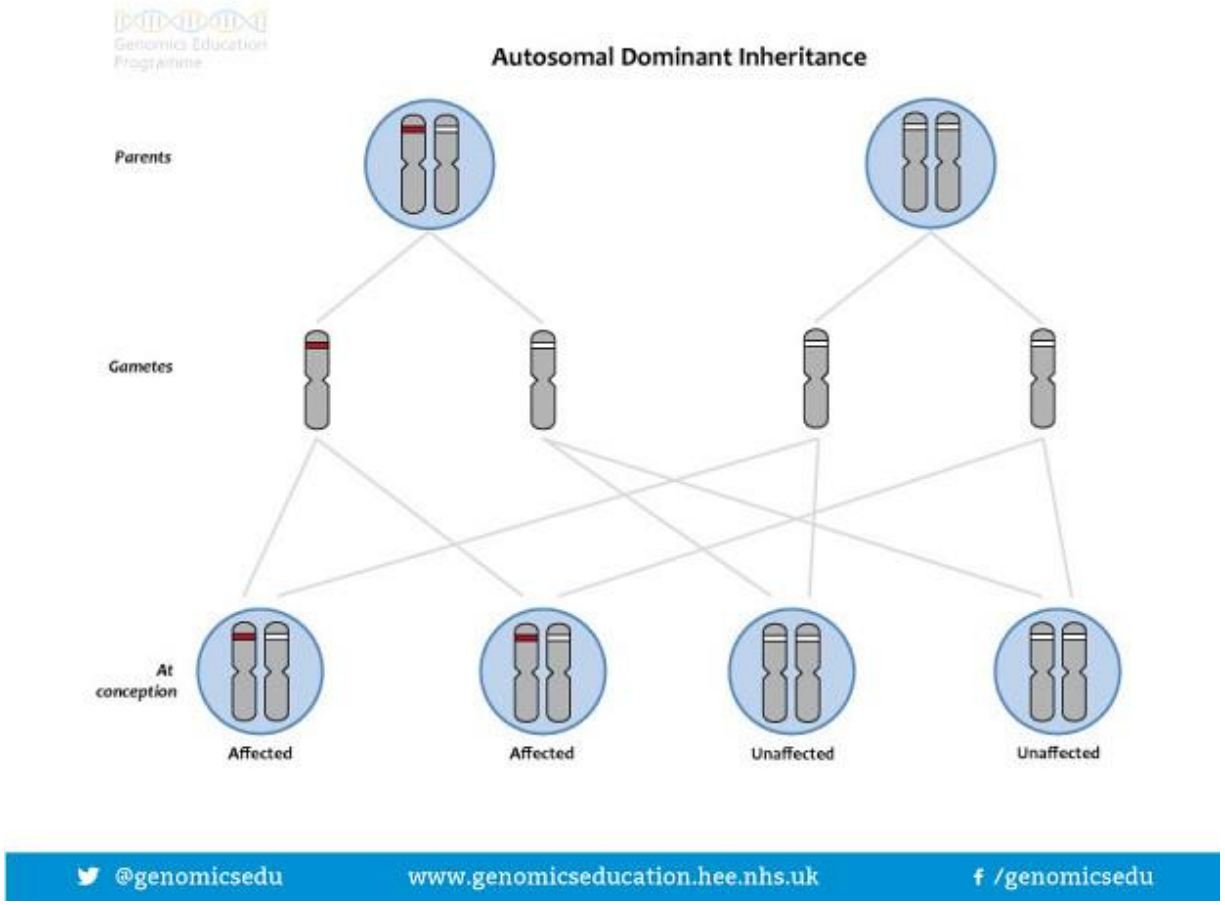


FIGURE 1

(A) FLAIR (B) T1 weighted showing proportionate dilatation of the ventricles and moderate cerebral atrophy

Case Study

- Genetics: *SCN1A* mutation positive (Dravet Syndrome)
- Inheritance pattern: autosomal dominant (1:2 or 50% chance)
- (?) to test parents – no information about the health history.
- Possible *de novo* mutation (i.e. new).
- Referral to clinical genetics for genetic counselling.



Case Study

- In UK, single gene testing is available provided there is clear phenotype (i.e. signs & symptoms) associated with Dravet.
- If the phenotype is heterogenous (i.e. syndromic) – may need chromosome testing (microarray) and/or whole genome sequencing.

R59 Early onset or syndromic epilepsy

Testing Criteria

Unexplained epilepsy with clinical suspicion of a monogenic cause including:

1. Onset under 2 years, OR
2. Clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome, OR
3. Additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital malformation), unexplained cognitive/memory decline

Testing may occasionally be appropriate where age of onset is between 2 and 3 years and following clinical agreement by a specialist MDT.

Overlapping indications

- R110 Segmental overgrowth disorders – Deep sequencing test should be used where megalencephaly is present to allow detection of somatic mosaic mutations

NOTE: If a metabolic disorder is suspected, testing should be carried out either using R89 or R98 or under an alternative metabolic-related clinical indication

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R59 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R59.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R59.3	Epilepsy - early onset or syndromic WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Genetic epilepsy syndromes (402)	WGS

Case Study

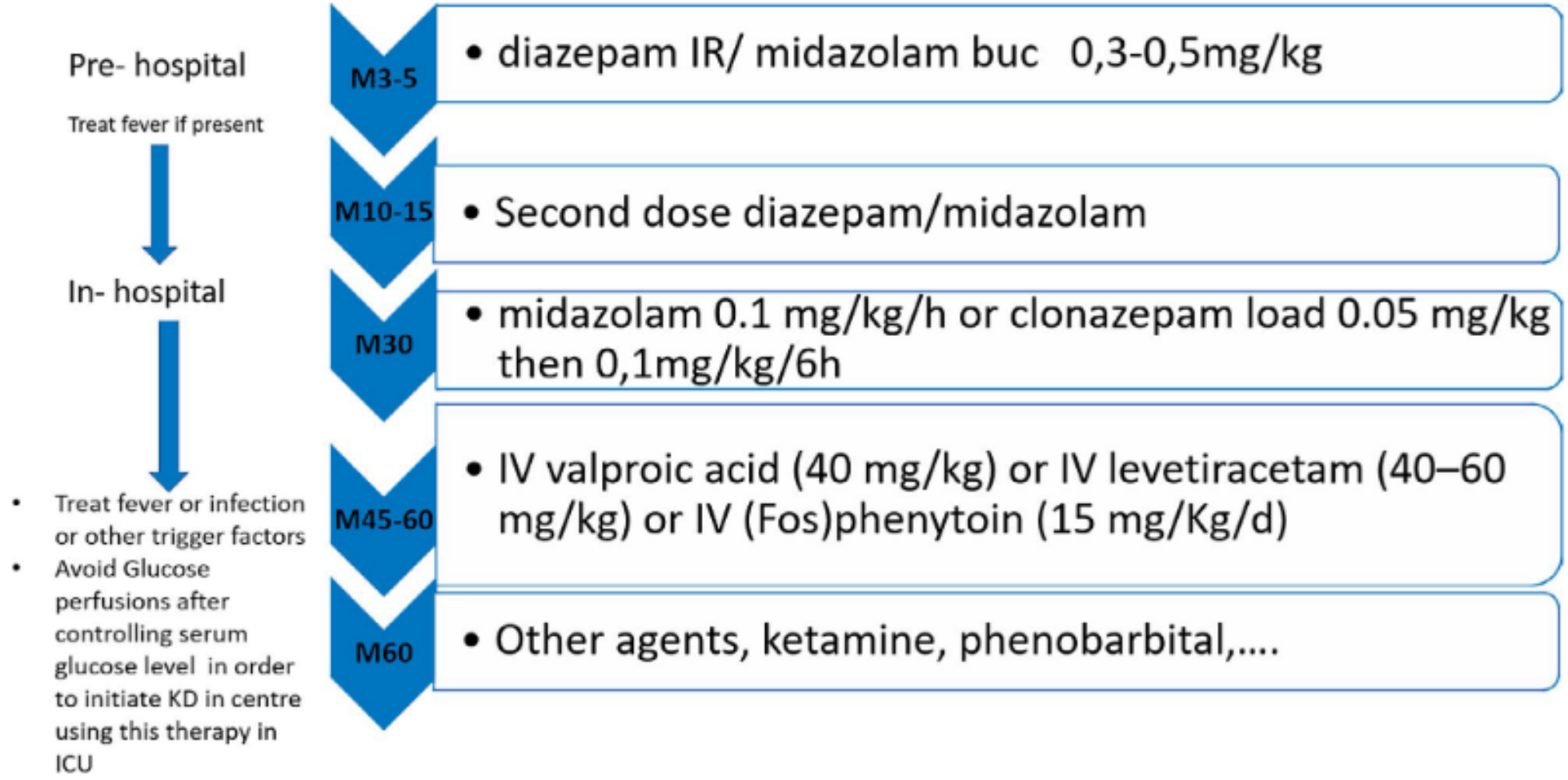
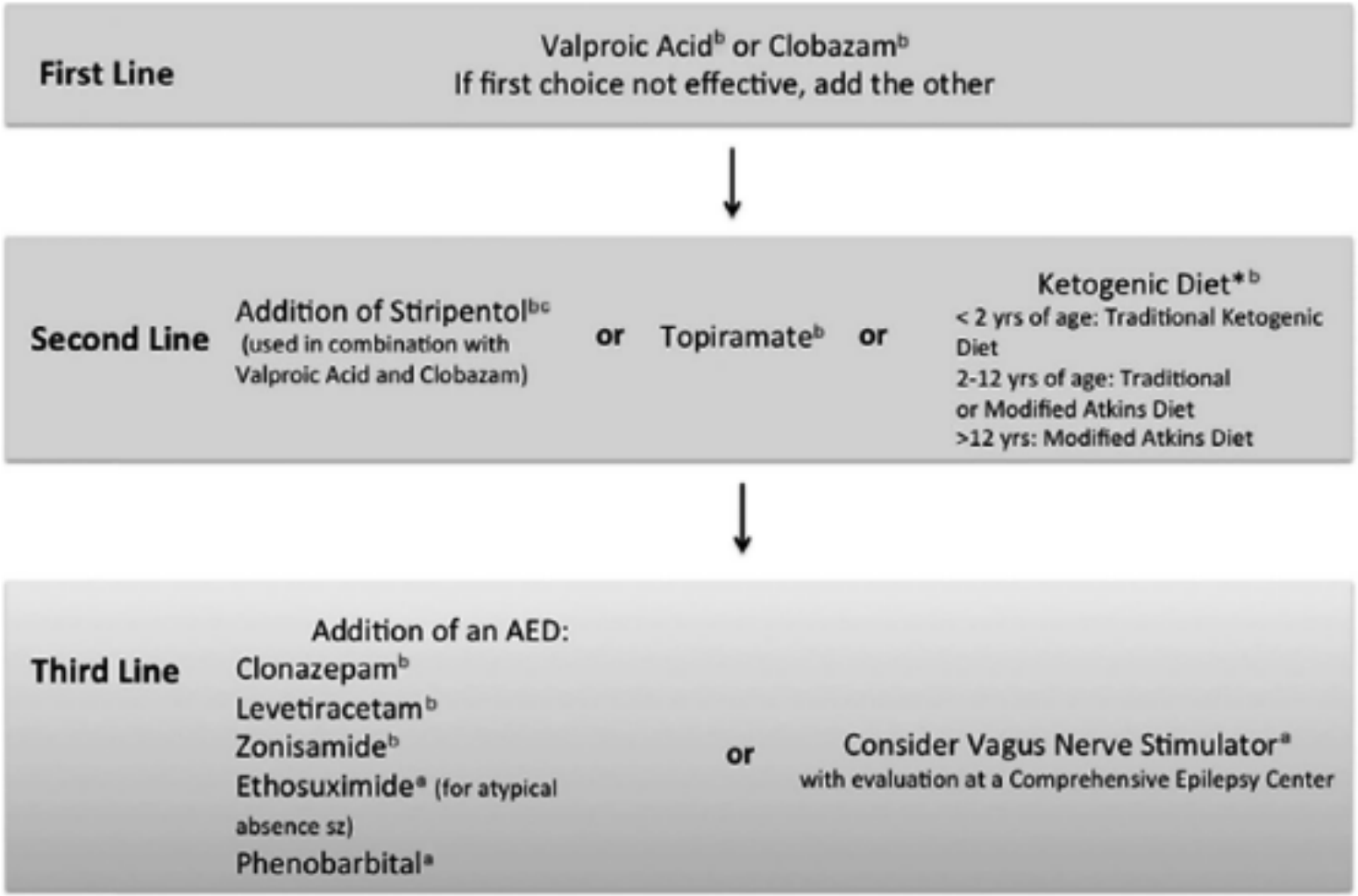


FIGURE 1 Proposed protocol for the treatment of prolonged seizures in association with Dravet syndrome. buc, buccal; ICU, intensive care unit; IR, intrarectal; IV, intravenous; KD, ketogenic diet; M, minute [Color figure can be viewed at wileyonlinelibrary.com]

Case Study

FIGURE 2 Treatment algorithm for Dravet syndrome as outlined by the North American consensus panel. Published with permission from Wirrell et al.[19] *Ketogenic diet is not suitable for all patients; its use is not required before moving to third-line therapies. [a]Agreed upon by moderate consensus. [b]Agreed upon by strong consensus. [c]Stiripentol is not approved for use in all jurisdictions. AED, antiepileptic drug; sz, seizures



Case Study

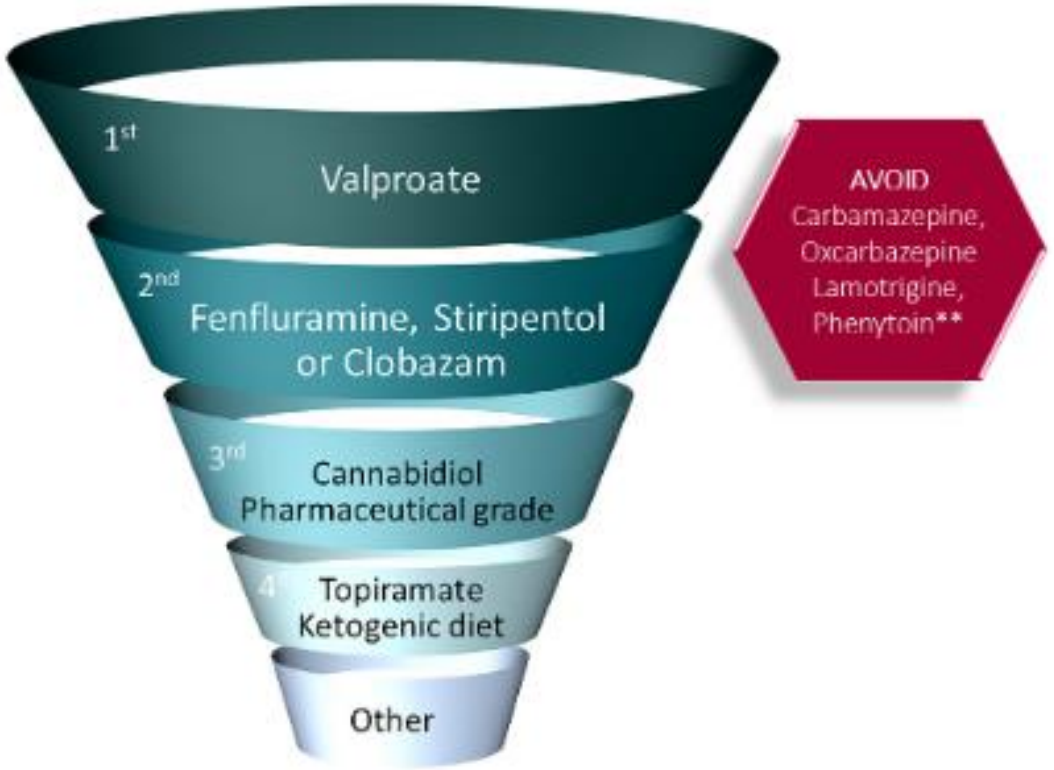


FIGURE 2 Therapeutic algorithm for maintenance therapies for management of seizures in Dravet syndrome. There was consensus for use of valproic acid as first-line therapy, and for use of clobazam, fenfluramine, or stiripentol as first- or second-line therapy. There was also consensus for contraindicated medications. **Phenytoin may be helpful for status epilepticus. "Other" includes vagal nerve stimulation, levetiracetam, zonisamide, bromides, clonazepam, and ethosuximide (for absences)

Useful Links

- Southeast Genomics – Rare Disease WGS
- Genomics Education Programme

Contact Details

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ResearchGate

Thank you

- Dr. Emma Matthews
- Dr. Elizabeth Caruana-Galizia
- Dr. Frances Elmslie
- Dr. Meriel MacEntagart
- Dr. Nayana Lahiri
- Dr. James Gratwicke
- Dr. Bridget Bax
- Dr. Michio Hirano
- Dr. Alan Pittman
- Dr. Kate Everett
- Dr. Kevin Blighe
- The Lilly Foundation
- Genetic Alliance UK
- Medical Research Council
- MD-UK & CMT-UK
- Epilespy Action
- Aderonke Adebiyi RN
- Tinashe Samakomva RN
- Dr. Tootie Bueser RN PhD
- Andrea Foreman CGC
- Heidi Brandon CGC
- Atkinson Morley Regional Neurosciences Medical and Nursing Staff
- St George’s Hospital NHS Foundation Trust.
- SGH Clinical Research Facility
- Genomics Education Programme
- Health Education England
- St George’s, University of London
- King’s College London
- Patient Advocacy Groups
- Patients