GEN PHILIC

Department of Biotechnology
Fergusson College (Autonomous),Pune.

Issue 4 | September 2020
Diseases | Disorders

Dr. Sonali Joshi
Head of The Department of Biotechnology

Dr. Gayatri Gurjar
Editor-in-Chief

Whom do your genes love more? Mom or Dad?

The Case Of Imprinted Genes

A child typically inherits two functionally active copies of a gene-one from mother and one from father.Imprinted genes differ from classical genes in this sense as only one functionally active copy is inherited from either parent and other is epigenetically silenced by a process called methylation leading to monoallelic expression.This in itself isn't a problem.The complication arises when the active gene is aberrant. Disorders like Prader-Willi syndrome, Angelman syndrome are associated with genomic imprinting.

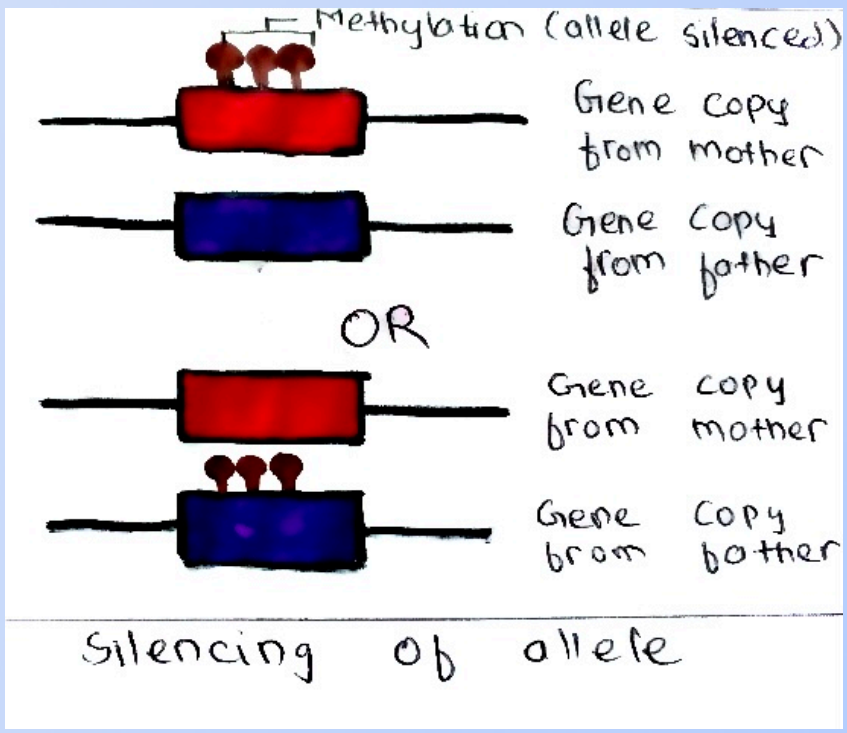


Illustration 1 : Silencing of allele

SNRPN CLUSTER

Some imprinted genes may cluster together.Why?Because genes too believe in 'sharing is caring'.They cluster and share the imprint control regions or IMRs-elements which controls them.One such cluster is snrpn cluster associated with Prader-Willi syndrome (PWS) and Angelman syndrome (AS). This cluster has an important gene UBE3A expressed only from maternal allele and it is imprinted only in the brain which correlates to the phenotype of PWS and AS patients. Two other important regions are AS imprint control (AS IC) and PW imprint control (PWS IC). These are differentially methylated in maternal allele and non methylated in paternal allele.

ANGELMAN SYNDROME

Characterised by puppet like movements and a happy diaposition, this disorder is maternally transmitted(as paternal gene is turned off) when there is a failure to express UBE3A.There a few reasons why this may occur:

1. maternal copy of 15q11-13 is deleted or inappropriately silenced.

2. AS IC is deleted which leads to unmethylation of imprint control (PWS IC), as methylation at PWS IC is laid down by AS IC. Therefore both alleles look like the

paternal one and unmethylation leads to snoRNA expression and no UBE3A in brain.

3. Uniparental disomy wherein only paternal alleles are inherited.

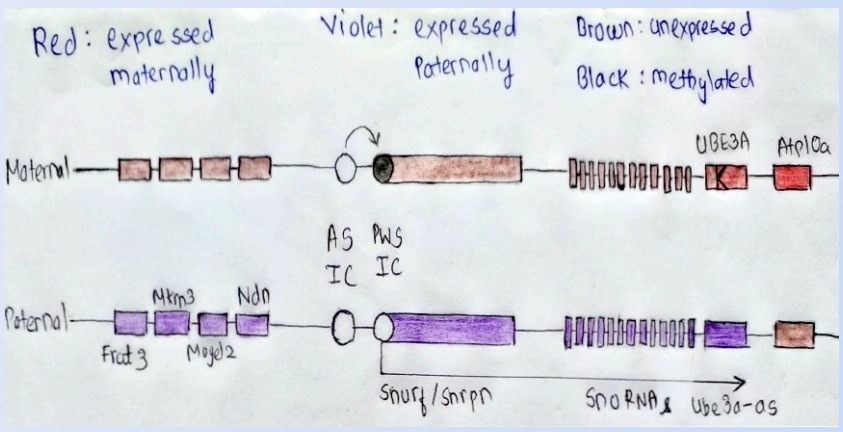


Illustration 2: Inheritance of Prader-Willi Syndrome

4. Mutations in UBE3A itself.

PRADER-WILLI SYNDROME

Characterised by low muscle tone and OCD this disorder is paternally transmitted. Causes of the disorder may be:

1.Deletion or inappropriate silencing of paternal copy of 15q11-13. Paternally expressed genes on this region like SNRPN, NDN genes and snoRNAs are not expressed.

2.Deletion of PWS IC leads to both alleles looking like maternal allele. Here too paternal genes are not expressed.

3.Uniparental disomy wherein only maternal alleles are inherited.

Mudra Deshpande
S. Y. BSc Biotechnology
(Editor)

Divya Bhardwaj
S. Y. BSc Biotechnology
(Editor)

As seen above absence of an alternate active gene to compensate for the disrupted allele can lead to severe disorders.These aren't driven by mutations in DNA sequence, rather the underlying machinery is largely an epigenetic one.Further research of the epigenome would lead to better treatment methods.

Article and illustrations by Isha Navare
F. Y. BSc. Biotechnology

Into the Brain of the Cell

Laminopathies: Genetic Disorders Caused By Mutation in Genes of Nuclear Lamina

The nucleus is the defining feature of eukaryotic cells and is separated from the cytoplasm by the nuclear envelope. The nuclear envelope is composed of a nuclear membrane, nuclear pore complexes (NPCs) and nuclear lamina. Laminas are nuclear proteins responsible for the structural organization of the nuclear envelope, nuclear lamina and chromatin in the metazoan nucleus. They are also implied to play a direct or indirect role in chromatin organization, regulation of replication and transcription, splicing, proper spacing of nuclear pore complexes, signalling, the connection between the nuclear skeleton and cytoplasmic skeletal structures, nuclear positioning, mechanosensing, and mechanotransduction.

History

In 1999, Bonne et al reported that mutations in LMNA encoding A-type laminas cause autosomal-dominant Emery–Derides muscular dystrophy. This opened the floodgates to discoveries over the next decade that mutations in the same LMNA gene which encodes largely ubiquitously expressed nuclear proteins (A-type lamins) causes more than a dozen diseases collectively called laminopathies like Cardiomyopathy dilated 1A, Congenital muscular dystrophy, Limb-girdle muscular dystrophy type IB, Charcot-Marie-Tooth Disease, Mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome, Atypical Werner syndrome, Lethal fetal akinesia, Restrictive dermopathy, Variant progeroid disorders, Lipoatrophy with diabetes and other features of insulin resistance.

Hypotheses

Two hypotheses, not mutually exclusive, have been formulated to explain why specific cells and in particular muscle and cardiac cells, are more sensitive to A-type lamina expression alterations: the '**structural**' hypothesis and the '**gene regulation**' hypothesis.

The 'structural' hypothesis suggests that mutated A-type laminas or the associated nuclear envelope proteins disrupt the integrity of the cell nuclear membrane, resulting in nuclear breakage and cell death in tissues exposed to mechanical stress, such as muscle fibers. Furthermore, laminas play a prominent role in nucleo-cytoskeletal coupling by the interactions with components of LINC (linker of nucleoskeleton to cytoskeleton complex).

The 'gene regulation hypothesis' suggests that A-type lamins are crucial in tissue-specific gene expression. Indeed, in Emery–Derides muscular dystrophy muscle, the transcriptional regulation is defective, likely due to a focal loss and disorganization of heterochromatin in fibroblast and muscle fiber nuclei. Interestingly, identification of the altered signalling pathway might represent a suitable target for a therapeutic intervention: treatments with rapamycin or MAPK inhibitors have been shown to improve symptoms in EDMD and dilated cardiomyopathy animal models.

Mutations in genes encoding nuclear lamins, cause a range of phenotypically diverse diseases. Research on pathophysiology using cellular and animal models subsequently has begun to catch up. A significant amount of current research is aimed at deciphering pathogenic mechanisms and some has connected mutations in LMNA to post translational protein modifications and alterations in cell signalling pathways that can be connected to pathophysiological processes and targeted by small molecule therapeutics.

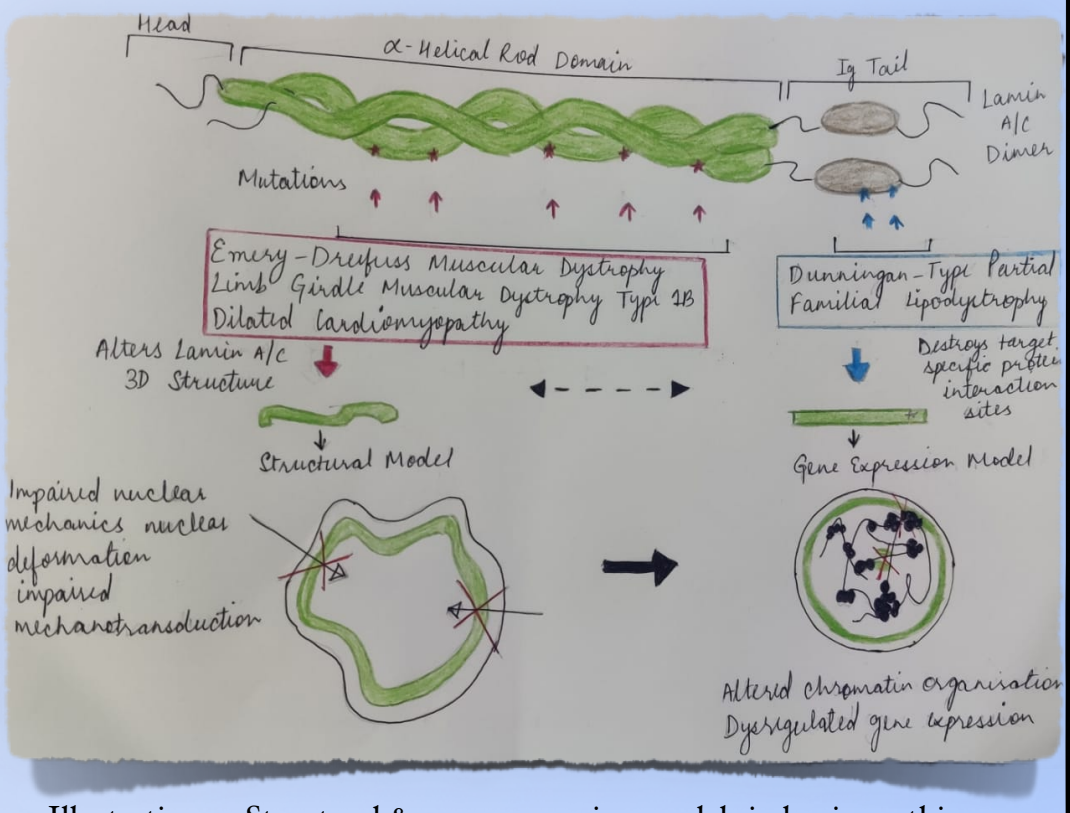


Illustration 3 : Structural & gene expression models in laminopathies

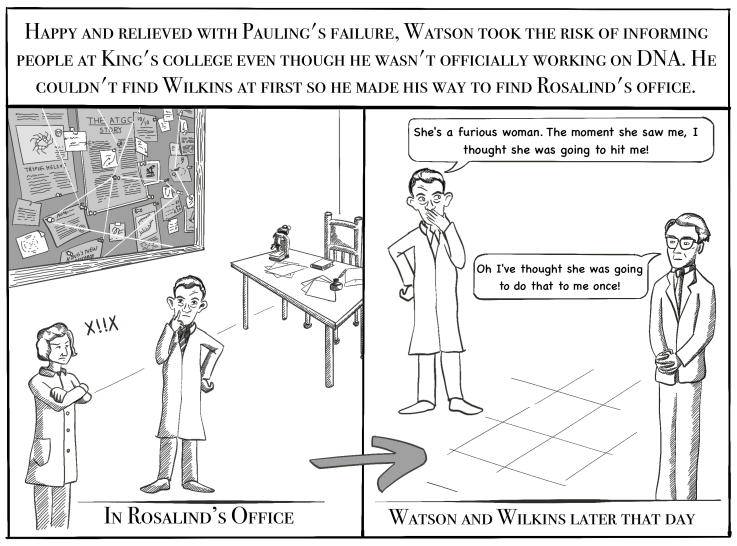
Illustration by : Roshni Rout
S. Y. BSc. Biotechnology

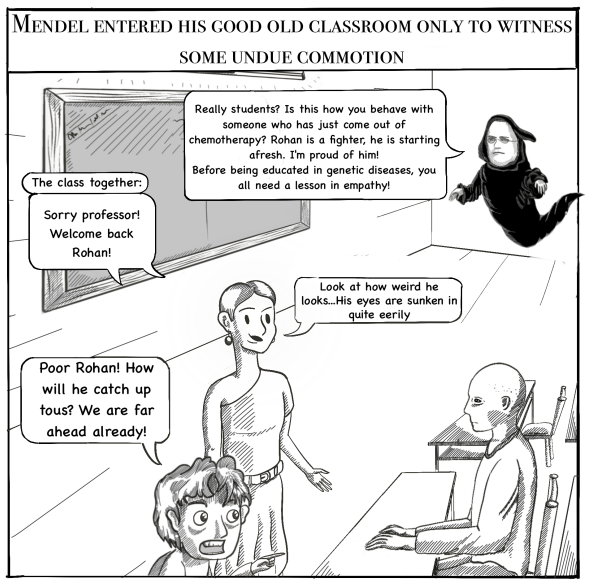
By Surabhi Verma
F. Y. BSc. Biotechnology

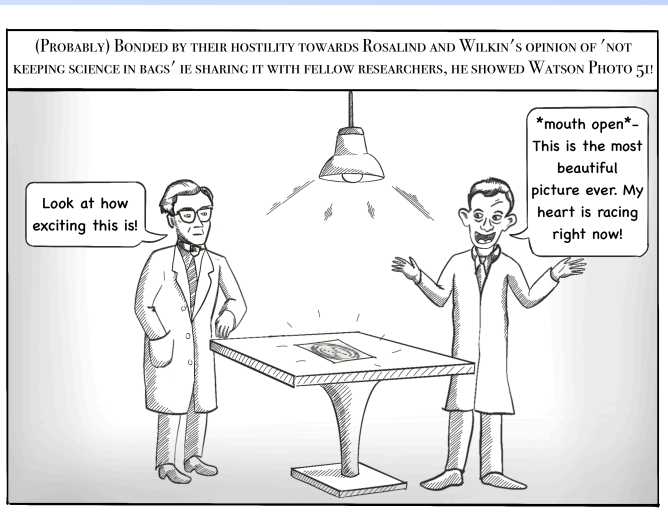
While laminopathies are rare diseases, the disease phenotypes that result from mutations in genes encoding lamins are common, such as dilated cardiomyopathy, insulin resistance and even ageing. In this regard, research on these fascinating rare diseases should provide insights into common disorders so as to find treatments and cure.

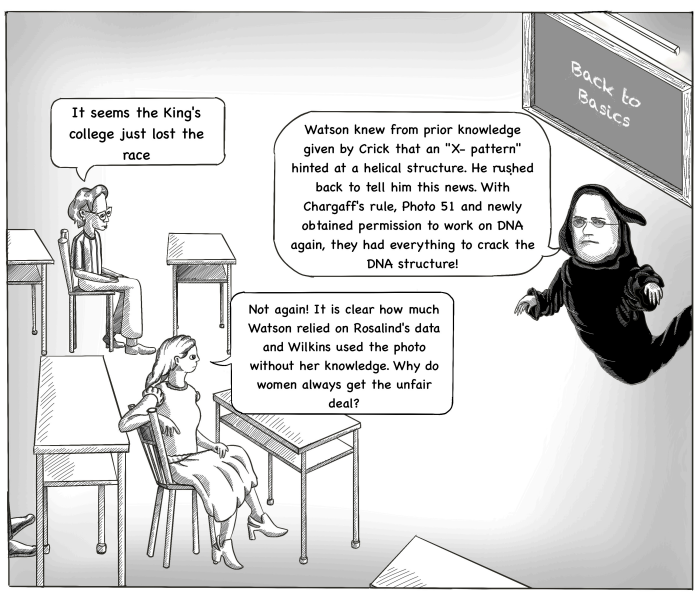
Back to the Basics with Friendly Ghost Grandpa Mendel!

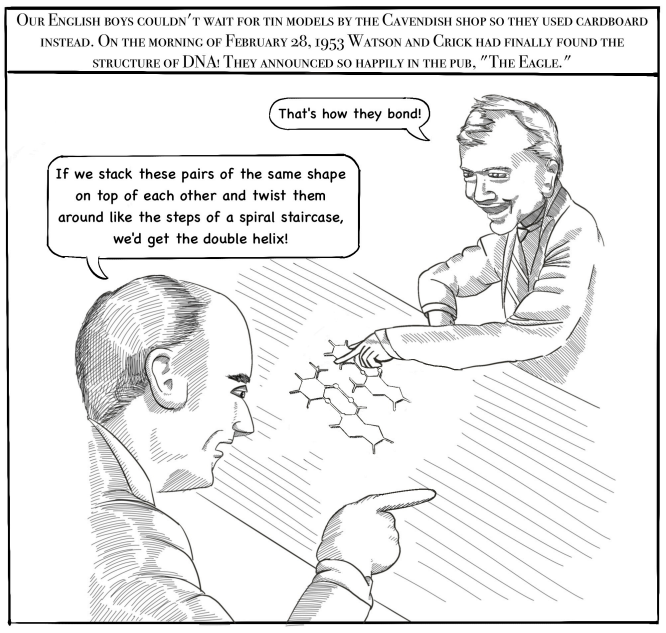
You know the legendary Gregor Mendel. You might not know the legends in the race to find secret of life! Come, discover the story with Mendel himself, and see where the journey takes you! (Note : Read left to right)

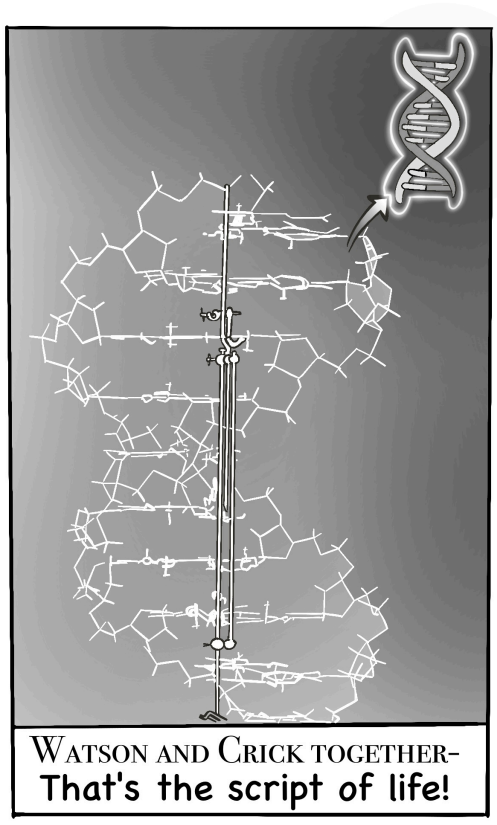












Epilogue

On April 25, 1953 the British scientific weekly *The Nature* published three papers one after the other-

1) 'A structure for Deoxyribose Nucleic Acid' by James Watson and Francis Crick.
2) 'Molecular structure of deoxypentose nucleic acids by lead author Maurice Wilkins.
3) 'Molecular configuration in sodium thymonucleate' by lead author Rosalind Franklin who had moved to Birkbeck College earlier that year because of her constant state of unhappiness and ill-treatment at King's College. Her famous Photo-51 was also published in this paper.

Almost a decade later, the 1962 Nobel Prize in Physiology or Medicine was awarded jointly to Crick, Watson and Wilkins. Notice how a member is missing here? Yes, due to Rosalind Franklin's unfortunate demise in April 1958, she was neither awarded nor given any recognition for her critical work on DNA. At mere 37 years of age, ovarian cancer took away her life but Watson's book, "The Double Helix" (1968) disrespected the very memory of her by depicting her as only Wilkins' assistant, incapable and unworthy of Nobel-Prize-calibre work. Both Francis Crick and Raymond Gosling criticised the book and felt that it provided an unfavourable portrait of none but Watson himself.

Among all the unsung heroes of this story- Rosalind Franklin, Erwin Chargaff, and Jerry Donahue (an officemate who pointed out how Crick was assembling the four bases wrong), Franklin definitely gets the worse end of the deal like many other women in science. Photo-51 was the main inspiration behind Watson-Crick's model and was used by them without her knowledge or permission.

However, many followers of her work have now come together to tell the story of this strong woman who fought sexism single-handedly up till her death; after which she continues to inspire many other women to fight for what is rightly theirs.

Author : Aarjvi Jain
S. Y. BSc. Biotechnology

Illustrator : Hrishikesh Hardikar
S. Y. BSc. Biotechnology

The powerhouse of the cell isn't perfect after all

Mitochondrial genome diseases

Descendants of ancient bacteria that took up residence inside an early eukaryote, mitochondria, sport their own genome and a distinct set of proteins, which are not coded by the genes in the nucleus. This popular evolutionary proposition was given by Lynn Margulis in the 1800s. Mitochondrial DNA (mtDNA) accommodates 37 genes that are all essential for its conventional functioning. 13 of these partake in the critical process of oxidative phosphorylation. Mutations here, can have devastating consequences including muscle weakness, seizures, movement disorders, learning disabilities and deafness. Not only these, but blemishes in mtDNA can lead to a range of perilous illnesses. "If you take all the mitochondrial diseases together, they are one of the most common causes of genetic diseases in humans." says molecular biologist,Michal Minczuk of the University of Cambridge, in the UK.

Diagnosis: Presence of the mutant mtDNA can be confirmed by using molecular genetic testing. But often, a more structured approach is required, such as the family history, cardiac evaluation, neuroimaging and CSF (cerebrospinal fluid) lactate concentration. Further investigation may include a series of different clinical tests, like muscle biopsy for respiratory chain function.

Treatment: Mitochondrial disease patients have mtDNA copies with or without the harmful mutations. Thus, it is pertinent to note that the ratio between the two varieties must reach a certain level before the symptoms occur. So, if this ratio was lowered below the specific threshold, the clinical manifestations might vanish. CRISPR (clustered regularly interspaced short palindromic repeats), the genome editor, celebrated as a potentially revolutionary biotechnology tool, isn't so omnipotent in this case. The reason being, it depends on an RNA strand to guide the DNA cutting protein to the right spot in the genome and most biotechnologists doubt that the mitochondria can take up these guide RNAs.

As an alternative, viruses that have lost their virulence and that are harmless, are being harnessed to ferry genes for the DNA-editing proteins into the cells. Why viruses? Its because of their innate property of fusing either directly into the plasma membrane (receptor-mediated fusion) or through the endocytic pathway.

In an experiment, the researchers injected recombinant viruses into the tail veins of a mutant mice. Once in the bloodstream, the viruses travelled to the heart, which harboured the defective mtDNA. When the scientists analysed the animal's cardiac tissue 65 days later, they found that the ratio of the faulty mtDNA, was about 40% lower. Upon measuring several metabolic molecules, it was revealed that the organism's power house of the cells, were working better! A safety trial of this innovative approach on humans, is their next aim.

Although the process of research in such fields is cumbersome, the ceaseless efforts put in, kindle a light of hope against the dark adversities of the mitochondrial disorders.

By Amulya Ichageri
F. Y. BSc. Biotechnology

Why and how do these mutations arise?

Genetic disorders which are caused due to mutations in the mitochondrial DNA are almost always inherited via maternal inheritance. This is because, only egg cells contribute mitochondria to the next generation and since these are provided by mothers, only females are able to pass mitochondrial mutations. Males on the other hand, while being capable of inheriting the mutations, cannot pass them on to the progeny.

Ø Mitochondrial inheritance

A few points need to be kept in mind while reading this article:

· Mitochondrial DNA varies immensely between unrelated families. Although, it is nearly identical among closely related individuals .

· An individual shares his/her mitochondrial DNA sequence with all of his/her relatives from the maternal lineage.

· For researchers, the process of obtaining and analysing mitochondrial DNA samples from deceased relatives becomes much more easier due to a cell containing much more copies of its mitochondrial DNA than its nuclear DNA.

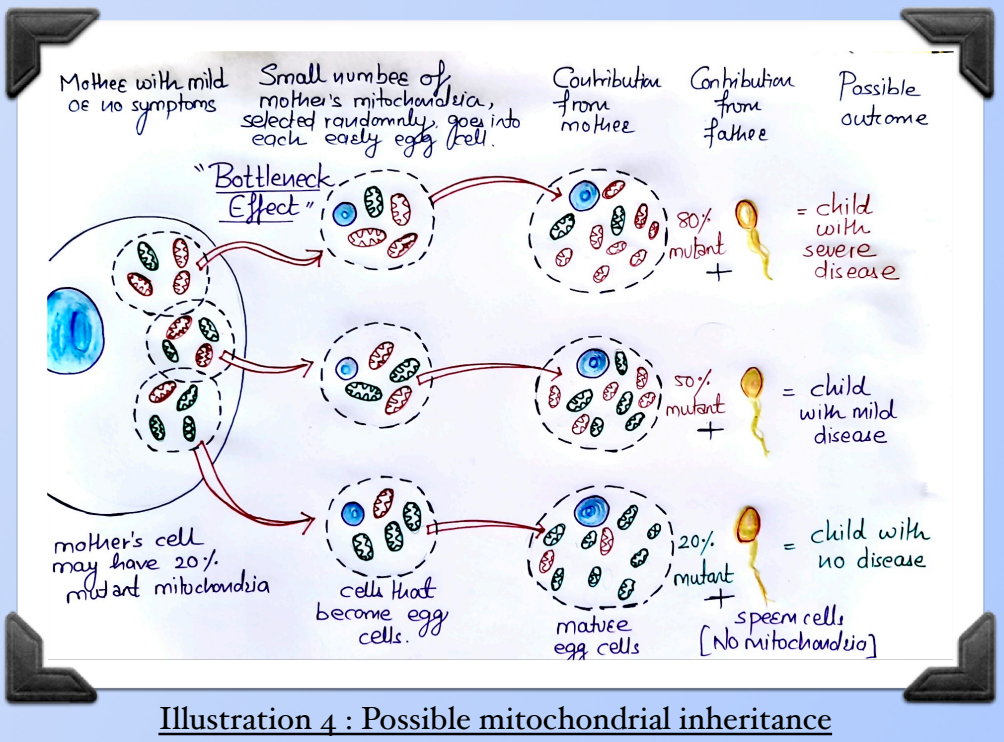


Illustration 4 : Possible mitochondrial inheritance

Almost all mtDNA diseases are maternally inherited diseases. You'd be surprised to know, there is an exception to this! To know how, check out the -facts or bonus section- of this article!

Ø ***Disease causing mutations are seen in mitochondrial DNA as well? No way!***

Mitochondrial DNA also undergoes a variety of mutations. In fact, it shows higher mutation rates when compared to nuclear DNA!

You might be wondering why do mitochondria have such a high mutation rate?

DNA polymerase gamma (POLG) is a nuclear gene that encodes the DNA polymerase responsible for replicating the mitochondrial genome. A

recent study suggests that a nucleotide imbalance might be present in the mitochondria which could lead to deceased POLG fidelity and higher mtDNA mutation rates.

We know for a fact that mitochondria generate reactive oxygen species (ROS) as a byproduct of oxidative phosphorylation. ROS production is not typical to the mitochondria. ROS production has been proposed to cause somatic mitochondrial mutations (somatic mutations occur in the DNA of certain cells during a person's lifetime and typically are not passed to future generations. This may lead to a continuous cycle in which generation of mutations increase due to ROS production, which In turn leads to the disruption and deregulation of respiration giving rise to the accumulation of even more mutations. In addition, the mtDNA also lacks the DNA repair mechanisms found in the nucleus.

Males afflicted with a mitochondrial disease are not considered to be a threat that can transmit the disease to the progeny. In a cell's mitochondrial DNA, heteroplasmic mutations arise frequently (heteroplasmy refers to the condition when some mitochondria in the cell have a mutation in the mtDNA, while some do not). Nevertheless, it is evident that homoplasmic mitochondrial mutations are transmitted to all the maternal offsprings (homoplasmy is when a cell carries uniform collection of mtDNA, it may either be completely mutant or completely normal).

During early development of the female germ-line, within each oocyte the count of mtDNA molecules gets reduced before it is amplified to reach a final count of about 100 000 in each mature oocyte. The variability between individual oocytes, and the different concentrations of mutant mtDNA seen in the offsprings of one woman is exactly because of this restriction and amplification. This is also called the mitochondrial 'genetic bottleneck'

Heteroplasmy is therefore a consequence of the genetic bottleneck.

However, a complex interplay between the mitochondrial and nuclear genomes has led to an extreme difficulty to predict disease outcomes, even with homoplasmic mitochondrial populations.

We now know that a mother with a mtDNA mutation will pass the mutation to all of her children. Despite this fact, not all of them will necessarily be symptomatic. Additionally, if the children do happen to be symptomatic, the percentage of mutant mtDNA in each part of the body will vary, indicating that the prognosis of the disease that each child has can be very different. This essentially will create an infinite number of manifestations of mitochondrial disease.

The different organs, and even adjacent cells within the same organ consist of different amounts of mutated mtDNA. This variability, along with the dependency of different organs on oxidative metabolism and also the tissue-specific differences indicates why certain tissues are preferentially affected in patients with mtDNA disease.

Mitochondrial mutations lead to more pronounced phenotypes in tissues having high energy demands, like, the brain, skeletal and cardiac muscles, etc because of the obvious fact that mitochondria functions as the powerhouse of the cell.

Mitochondrial disorders often involve the neuromuscular system; may include encephalopathy, myopathy (muscle weakness), ataxia(loss of control on bodily movements), retinal degeneration, and loss of function of the external ocular (eye) muscles.

Health consequences of inherited mitochondrial DNA mutations vary widely, but commonly observed features include:

1. **Central nervous system** – Encephalopathy, stroke-like episodes, seizures and dementia, ataxia, migraine
2. **Muscular system** – Muscle weakness and wasting
3. **Eye** – External ophthalmoplegia, cataract, pigmentary retinopathy
4. **Hearing** – Bilateral sensorineural and deafness
5. **Heart** – Cardiomyopathy, heart block, pre-excitation syndrome
6. **Renal** – Renal tubular defects
7. **Endocrine** – Hypoparathyroidism, hypothyroidism, gonadal failure
8. **Intestinal** – Dysphagia, constipation and hepatic failure
9. **Peripheral nervous system** – Myopathy, neuropathy.

It is observed that mitochondrial mutations might also contribute to a number of common clinical disorders such as diabetes, Alzheimer's and Parkinson's disease. Diabetic patients who have mutations in mtDNA, largely show an impaired pancreatic β-cell insulin secretion. More than 20 mtDNA mutations are known to be associated with diabetes. Among these, the mtDNA mutation that is frequently encountered is the A to G replacement at position 3243 (A3243G), which encodes leucyl-$tRNA^{UUR}_{23}$ (of mitochondria)

-A scientific concept never makes sense without examples. So here are some examples to guide you with the understanding of mitochondrial inherited diseases : MERRF (myoclonic epilepsy with ragged red fibres) syndrome, NARP (neuropathy, ataxia and retinitis pigmentosa), Pearson syndrome, Rhabdomyolysis, etc. These conditions essentially lead to defects in the nervous system and muscles.

Is Paternal inheritance of mitochondria possible ?

A new study found rare cases of mitochondrial DNA (mtDNA) being passed down from fathers in three unrelated families. The team, from the U.S, China and Taiwan identified 17 cases from three unrelated multiple-generation families with a high level of mtDNA heteroplasmy (24-76%)

Prior research has shown that the mtDNA of sperm cells is destroyed once an egg becomes fertilised. As such, the scientists hypothesised that some males may carry mutations that prevent their mtDNA from being destroyed and affect mtDNA replication, which would increase the abundance of paternal mtDNA and help explain their findings.

Thus we can conclude that: "Although the central dogma of maternal inheritance of mtDNA remains valid, there are some exceptional cases where paternal mtDNA could be passed to the offspring", the scientists wrote.

Interesting fact

The mutation rate in mtDNA is 10-17 fold higher than in nuclear DNA!

Leigh syndrome

Leigh syndrome is another example of mitochondrial inheritance disorder. Out of all the people affected, about 20% of people had Leigh syndrome due to a mutation in mtDNA. Most of the genes associated with Leigh syndrome show modified abnormal phenotypes in the process of energy production in mitochondria, especially in the proteins in the complexes of oxidative phosphorylation which leads to the disruption of the assembly of the complexes and eventually ATP deficiency. Disruption of complex I is the most common cause of the syndrome. Overall phenotype/ symptoms of this condition include motor and intellectual regression. Death usually occurs within 2 years of onset (usually after birth).

Relation between Mitochondrial DNA mutations and aging and cancer

Research suggests that due to ROS production, the progressive accumulation of these mutations over a person's lifetime may play a role in the normal process of aging. The cells having increased production of ROS in their mitochondria experience a decreased metabolic function and energy production, increased cell death and a decreased capacity to replicate the genome.

Surprisingly, scientists found a link between the buildup of these somatic mutations and some forms of cancer. A study carried out by Polyak and colleagues (1998) suggests that the somatic mitochondrial mutations might have provided a growth advantage to a single cell. This cell might have subsequently proliferated more rapidly than the surrounding cells. Furthermore, there can be a possibility of the mutation providing a replicative advantage to the mutant mitochondrial genome, the scientists said, keeping in mind the homoplasmic nature of the mitochondrial DNA mutation. With this, an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease has hence been observed.

Despite the diminutive size of the mitochondrial genome, mtDNA mutations prove to be crucial cause of inherited diseases. In recent research years, we have witnessed a considerable amount of progress in understanding basic mitochondrial genetics and the relationships between inherited mtDNA mutations and various disease phenotypes. Moreover, the discovery of involvement of mtDNA mutations in aging and cancer kept scientists astonished! However, many more challenges still linger, including the prevention and treatment of these diseases.

Article by: Sanskruti Deshmukh
S. Y. BSc. Biotechnology

And (along with illustrations) Aqsareha Mujawar
S. Y. BSc. Biotechnology

Fickle mind? Check them genes!

Genetics of Psychiatric Disorders

New studies show that major mental disorders, traditionally thought to be distinct, share certain genetic glitches. Scientists have long recognised that many psychiatric disorders tend to run in families, suggesting potential genetic roots. Such disorders include autism, attention deficit hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder and schizophrenia.

Psychiatric genetics is a branch of behavioural neurogenetics and it studies the role of genetics in the occurrence and development of mental disorders. There are certain genetic factors that contribute to the development of mental disorders. These include epigenetic regulation, genetic polymorphisms and single gene changes. Psychiatrists have been using tools of molecular biology to understand the mechanisms of a wide variety of complex mental disorders to learn about their heredity patterns and to improve and develop novel treatment methods.

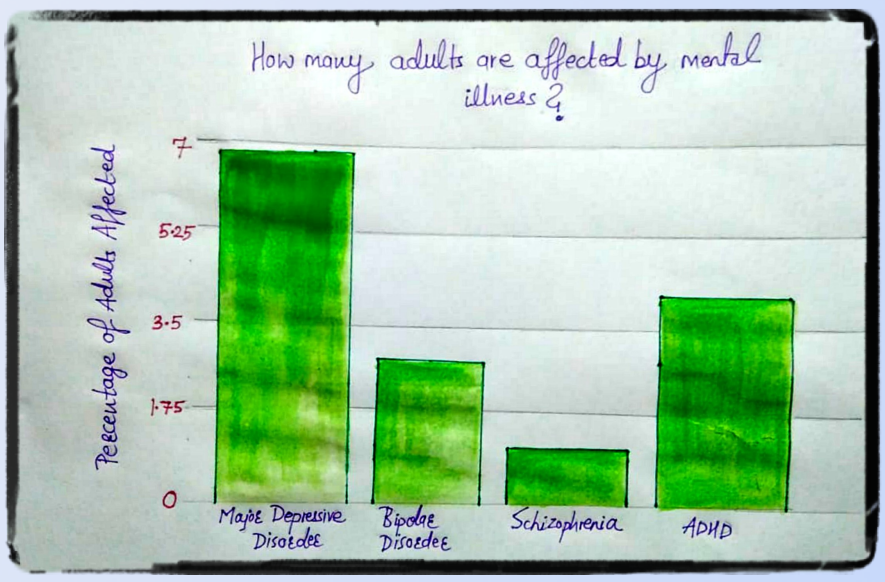


Illustration 5: Prevalence of mental illnesses in adults

Illustration by : Aqsareha Mujawar
S. Y. BSc. Biotechnology

The traditional methods for studying psychiatric disorders include family study, adoption study, twin study and so on. Newer methods include molecular genetic studies of mental disorders, the goal of which is to identify and clone genes that contribute to the risk of such disorders, influence their course or promote resilience. Genetic information is coded along the length of the DNA, the chemical basis of heredity and is organised into genes, the fundamental units of genetic information. Variations in the DNA sequence called polymorphisms can be heritable thus may be the cause of certain diseases. Along with heritable polymorphisms, deletions, insertions and rearrangements of DNA and also mutations can all cause changes in gene expression and result in disease. The latest molecular methods to study psychiatric genetics are as follows:

1. **Linkage Study:** Linkage analysis is an approach for locating a disease gene in humans. It uses DNA sequences with high variability (i.e., polymorphisms) in order to increase the power to identify markers that are associated with a disease within families. Linkage studies employ restriction fragment length polymorphisms (RFLPs) or single nucleotide polymorphisms (SNPs) to track diseases in families.

2. **Gene Mapping:** Techniques involving cloned DNA are used to locate genes to specific regions of chromosomes, to identify the genes responsible for diseases and to study how faulty gene regulation causes a particular disease. Gene localizing thus defines a map of the human genome and can be accomplished by two techniques, somatic cell hybridization and in situ hybridization.

3. **Association Study:** Association studies are used in cases of psychiatric disorders due to the complexity of the disorder. An association study design compares the frequency of marker genotypes. There are two common approaches to association studies, case-control designs and family-based designs. In a case-control study, allele frequencies are compared between a group of unrelated affected individuals and a matched control sample. In a family-based design study, the mother, father and the affected offspring are investigated and allele frequencies in the transmitted and non-transmitted chromosomes (chromosomes which are not inherited from parents) are examined.

Let us look into the genetic architecture of some common psychiatric disorders:

1. Autism: The genetics of autism are complex and it is unclear whether autism spectrum disorder (ASD) is explained more by multigene interactions or by rare mutations with major effects. Scientists report that they used genome sequencing to identify 69 genes that increase the risk of autism spectrum disorder. Recent researchers have identified roles of exon mutations in sodium channel protein type 2 subunit alpha, katanin p60 subunit A-like-2 and chromodomain helicase DNA-binding protein 8 in the pathogenesis of ASD.

2. Schizophrenia: Evidence suggests that genetic vulnerability due to multiple genes along with environmental factors can act together, resulting in the development of schizophrenia. The risk of developing schizophrenia increases ten-fold if there is an affected first-degree family member. Genome-wide association studies have discovered uncommon copy number variations (mainly deletions) and common SNPs with alleles are associated with schizophrenia. A novel association for schizophrenia is in Ensembl gene, which encodes the primary transcript for the microRNA137 (MIR-137) which is a key regulator of neuronal development and is highly expressed at synapses in the cortex and hippocampus.

3. Bipolar Disorder: Novel genes have been identified as possible contributors to bipolar disorder, also known as manic-depressive illness. Bipolar disorder may run in families and risk factors for developing the disease increases if there's a first degree relative who is affected. Recent studies have found that the gene "ADCY2" on chromosome five and the so-called "MIR2113-POU3F2" region on chromosome six and three risk regions, "ANK3", "ODZ4" and "TRANK1", were confirmed to be linked to bipolar disorder. The genome-wide association studies revealed voltage dependent calcium channel, alpha 1C subunit (CACNA1C), which regulate neuronal excitability may also act as a factor for developing the disorder.

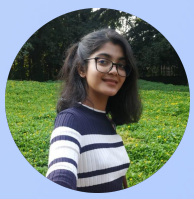
4. Alzheimer's Disease: Rare autosomal dominant mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and PSEN2 are known to cause early-onset familial Alzheimer's disease. Recently, around ten loci have been identified that accounts for ~ 33% of the risk attributable to genetic effects, with the major contribution being from apolipoprotein E (APOE) in Alzheimer's disease.

In recent studies, a lot of other psychiatric disorders like eating disorders, obsessive-compulsive disorder (OCD), panic disorder, tobacco and alcohol abuse and generalised anxiety disorders have all been associated with abnormalities in genes and thus, their inheritance and development.

Psychiatric genetics has generated very promising results in terms of risk variants associated with major psychiatric disorders and treatment outcome. The identification of risk-conferring genotypes at certain loci will provide informative independent variables capable of revolutionizing the ability to classify mental disorders, increase diagnostic yield and as a result devise novel treatment procedure. These approaches will provide a more unified understanding of neural mechanisms involved in human behaviour and its disruption in psychopathologies. Such an approach may open up new avenues for therapeutic intervention for clinical populations at the pharmacological, genetic and behavioural levels and identify windows of development that may be most optimal to treatment.

By Sifa Lalani
S. Y. BSc. Biotechnology

And Pragyananda Choudhury
S. Y. BSc. Biotechnology



A fear that still haunts

Uncovering mysteries of cancer

As the average life expectancy of human increases with the advancement in medical technology, so do the changes of having cancer, which generally comes with age. Cancer is a disease wherein cells divide uncontrollably and deprive the surrounding tissue of necessary resources by diverting them to themselves. The situation is still under control when it comes to benign tumor (which does not invade nearby tissues), however, the moment the tumor turns malignant, chaos ensues and chances of survival dwindle. All hope is not yet though, researches have now come up with some promising technique which involves addition and deletion of certain genes in an individual genome so as to control the proliferation of cancer and discover new anti-cancer drugs.

1) A study in mice suggests some cancers are addicted to having extra chromosomes.

It is found that many cancer cells carries an extra copy of a particular chromosome or a part of it and that this extra part is essential for the cancer cells to keep growing. Scientists of Cold Spring Harbor Laboratory in New York, developed a method for removing that extra chromosome or the extra part which was accelerating the growth of cancer cells in an ovarian cancer called as A2780 which carries an extra long arm of chromosome 1 also known as 1q. Scientists carried out an experiment in which they removed this extra long arm of chromosome from the cancer cells and then compared the growth of original and 1q derived cancer cell in lab dishes when transplanted into animal model system(mice). Scientists found out that cells with surplus

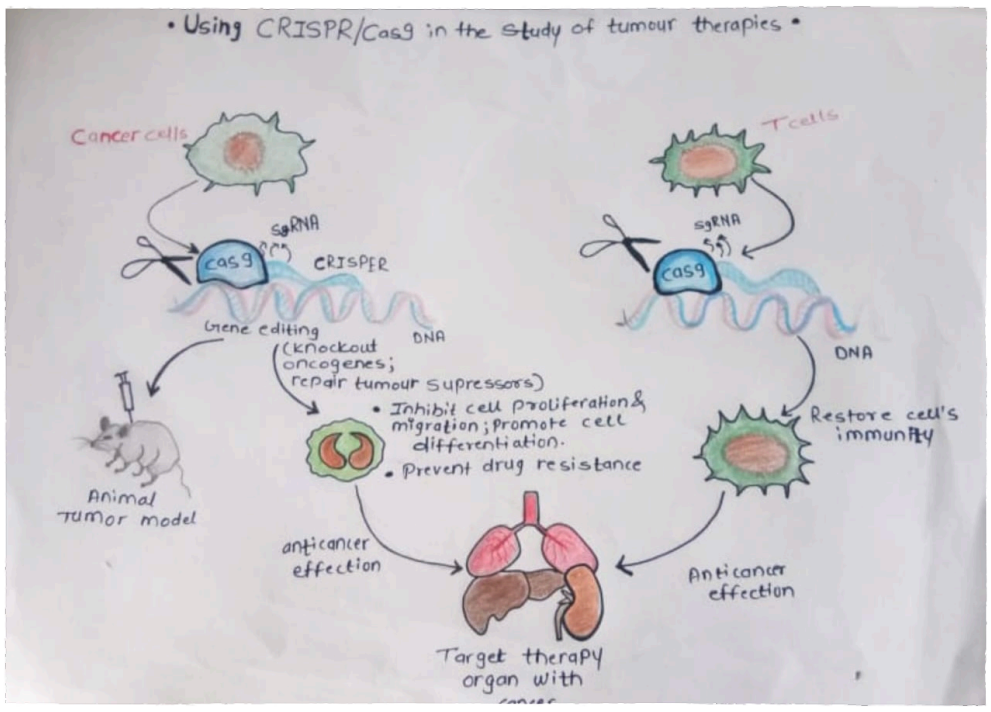


Illustration 6 : CRISPR/Cas9 in the study of tumour therapies.

Illustration by : Divyashi Motwani
S. Y. BSc. Biotechnology

chromosomes formed many colonies (tumours) while the cells from which scientists removed the 1q arm hardly grew at all. "They've almost entirely lost their ability to exhibit malignant growth," commented one of them. Interestingly these cells somehow managed to get back their lost surplus chromosomes restoring the cell's growth . So finding out which genes turn cancer cells into addicts is necessary if one wants to develop an anti-cancer drug. Following this idea, the scientists looked for the gene which was tempting the cells to regain that surplus chromosomes. They discovered one gene called MDM4, which was inhibiting the activity of p53(A protein that acts as a tumour-suppressor). Through further experimentation, it was figured out that as the amount of MDM4 increases the activity of p53 protein gets reduced allowing cancer cells to keep growing. To confirm the role of MDM4 in cancer promotion and confirm their hypothesis, the scientists removed the MDM4 gene from that surplus chromosome via popular technique known as CRISPR/Cas9. Their hypothesis was proven correct by the observation that the cells lacking the third copy of MDM4 formed very few colonies as compared to the cells housing three copies of it. Scientists further stated that gene MDM4 isn't the only one spurring the growth but this study definitely showed us the path toward a new drug discovery.

Scientists explain that It is very complicated to locate the genes which affect the growth of cancer cells but this study definitely showed us that in future it is possible to locate the genes which are inhibiting or promoting the cancer cells to grow and this ultimately help us in treating various types of cancers.

2. Another research has been performed which shows a promising path to new anti-cancer drugs.

A study conducted in Fels Institute of Cancer Research and Microbiology conveyed that the patients who were suffering from prostate cancer and carrying only one copy of PPP2R2A gene on chromosome 8, do not survive as long as the patients whose tumours have two copies of the same. It was later determined, that the reactivation of PP2A (Protein Phosphatase 2A) in the cell deficient of PPP2R2A stops and even kills the cancer cells in animal based model . Scientists ascertained that as cells lose PPP2R2A gene, they show rapid cell division and replication thus generating more and more cells (which is a characteristic of cancer cells) and these cells gets breezed through mitotic checkpoints (which ensure the proper orientation of chromosomes for cell division). However, the reactivation or restoring of PP2A protein, results in incitement of mitotic checkpoints and ultimately causes weakening of centrosome. Thus, the combined whammy of activation of mitotic checkpoints and weakening of centrosome results in collapse of mitotic spindle apparatus, with chromosomes not knowing where to go and ultimately causes the death of cell. Small molecules that activate PP2A in the cancer cells and that have the potential of being developed into drugs have already been identified.

It is reassuring to know that the 'Eurekas' in cancer research have not halted. Scientists heavily invested in cancer research have made statements saying that while more experiments are required to find a specific anti-cancer drug, promising results make themselves known such, that the future having having a specific drug may not be far.

By Ayush Punwatkar
T. Y. BSc. Biotechnology

The Merry Game-te Corner

1. Code Decode

Fill in the blanks and unjumble the highlighted letters to decode the word of this issue.

i. First hereditary condition cured by gene therapy: _ _ _ _ _ _

ii. In 1963, Stephen Hawking was diagnosed with: _ _ _

iii. Abnormalities in the genome cause a: _ _ _ _ _ _ _

iv.2n+1 is the condition for: _ _ _ _ _ _

v. The inborn metabolism error that causes decreased metabolism of phenylalanine: _ _ _

Word of the Issue: _ _ _ _ _ _

2. Heredity Hunt

Find the words listed in the word search below:

DISABILITY
AUTOSOMAL
CONGENITAL
DOWN
PLOIDY
HAEMOPHILIC
DEFECT
SYNDROME
MUTATION
CANCER

M	P	J	C	K	C	R	O	L	H	M	Q	K	D	N	F	A	H	P	E
E	V	B	O	O	M	N	A	A	S	A	K	S	K	C	W	J	E	T	S
Q	O	I	N	T	U	M	D	U	Y	B	E	L	S	I	N	E	J	O	K
A	H	G	G	O	T	O	P	T	N	K	L	M	K	W	J	U	Y	I	R
K	X	P	E	A	A	L	I	O	D	N	M	K	O	L	L	M	Z	J	I
O	L	Q	N	P	T	S	Y	S	R	S	I	D	E	P	S	C	H	A	R
T	J	L	I	L	I	A	T	O	O	U	T	B	B	L	H	B	T	N	E
C	U	Z	T	B	O	J	L	M	M	S	N	I	E	O	K	I	E	E	C
E	C	I	A	R	N	V	W	A	E	H	I	N	S	I	R	M	L	H	N
F	W	S	L	E	T	K	I	L	F	L	S	A	N	D	J	U	J	I	A
E	I	E	S	D	U	G	Q	Z	A	Z	K	Y	U	Y	Q	E	X	W	C
D	K	L	I	O	M	X	J	S	P	D	A	L	Q	V	A	J	W	T	S

3. Gags By Gregor

Q. What do you call an acid with an attitude?

A. A- Mean-oh-Acid

Created by : Divya Bhardwaj
S. Y. BSc. Biotechnology

How did you find it? Any feedback? Suggestions?

We would like to know what you thought of this issue of Genophilic, any suggestions are welcome.

Our next issue will be on the topic 'Genetic variation and evolution', and we would appreciate any contributions on said topic.

Contact us on : editor.genophilic@gmail.com

References

The Case Of Imprinted Genes

1. https://www.nature.com/scitable/topicpage/imprinting-and-genetic-disease-angelman-prader- willi- 923/#:-:text=Over%20the%20years%2C%20a%20number, %2C%20and%20Beckwith%2DWiedemann %20syndrome
2. https://www.nature.com/scitable/topicpage/genomic-imprinting-and-patterns-of-disease- inheritance-899/
3. https://ghr.nlm.nih.gov/primer/inheritance/updimprinting
4. https://www.coursera.org/lecture/epigenetics/4-5-snrpn-icr-mechanism-prader-willi-and- angelman- syndromes-iZoit

Laminopathies: Genetic Disorders Caused By Mutation in Genes of Nuclear Lamina

1. https://cmbl.biomedcentral.com/articles/10.1186/s11658-018-0093-1
2. https://onlinelibrary.wiley.com/doi/full/10.1002/path.2999
3. https://journals.physiology.org/doi/full/10.1152/physrev.00047.2005
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5040975/
5. https://www.ncbi.nlm.nih.gov/books/NBK6151/

3. Neuroscience

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4228562/
2. https://www.who.int/bulletin/archives/78(4)455.pdf https://en.wikipedia.org/wiki/ Heritability_of_autism
3. https://www.nih.gov/news-events/nih-research-matters/common-genetic-factors-found-5-mental-disorders#:~:text=Scientists%20have%20long%20recognized%20that,disorder%2C%20major% 20depression%20and%20sc
4. hizophrenia.
5. https://en.wikipedia.org/wiki/ Psychiatric_genetics#:~:text=Psychiatric%20genetics%20is%20a%20subfield,bipolar%20disor
6. der%2C%20and%20autism).

4.1. Mitochondrial genome diseases

1. https://ghr.nlm.nih.gov/mitochondrial-dna https://my.clevelandclinic.org/health/diseases/15612-mitochondrial-diseases https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4788752/?report=classic https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting https://www.genome.gov/genetics-glossary/Mitochondrial-DNA

4.2 Mitochondrial genome diseases

1. https://www.nature.com/scitable/topicpage/mtdna-and-mitochondrial-diseases-903/#
2. http://hihg.med.miami.edu/code/http/modules/education/Design/CoursePageContent.asp? ID=20
3. http://hihg.med.miami.edu/code/http/modules/education/Design/Print.asp? CourseNum=2&LessonNum=4
4. https://ghr.nlm.nih.gov/primer/mutationsanddisorders/mitochondrialconditions
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1762815/ https://rarediseases.info.nih.gov/diseases/7048/mitochondrial-genetic-disorders
6. https://www.umdf.org/what-is-mitochondrial-disease/inheritance-and-genetics/#:~:text=All%20maternally%20inherited%20diseases%20are,from%20the%20mother%20 and%20father.
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020716/
8. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(99)90244-1.pdf
9. https://ghr.nlm.nih.gov/condition/leigh-syndrome#inheritance https://slideplayer.com/slide/4088689/

5. Uncovering mysteries of Cancer

1) https://plan.core-apps.com/ascbembo2019/abstract/c
2) 2) https://www.sciencenews.org/article/surplus-chromosomes-may-fuel-tumor-growth- some-cancers
3) 3) https://onlinelibrary.wiley.com/doi/full/10.1111/cge.13589
4) 4)https://www.templehealth.org/about/news/common-genetic-defect-in-prostate-
5) cancer-inspires-path-to-new-anti-cancer-drugs
6) 5) https://cancerres.aacrjournals.org/content/76/14_Supplement/3662