The Department of Biochemistry

Sri Venkateswara College, University of Delhi

# Expressions

Year 2021-22



EPIGENETICS

# From the Editor's Desk

Ananya Bandyopadhyay

It brings me immense joy to present this year's departmental magazine, Expressions 2022, the theme being 'Epigenetics'.

Epigenetics has been a part of our curriculum and exposure to this fascinating superimposition of information over our genetic code really caught our imagination. Thus came the collective thought to make it the theme for this year's Expressions. The significance of epigenetics has grown by leaps and bounds in recent times with the advent of the innovative method of Methylscape.

Designing and publishing a magazine, including but not limited to layout design and choice of suitable content, calls for a lot of dedicated teamwork. Doing it online makes the challenge even more daunting and so we consider ourselves lucky that offline activity opened up at the right time. In fact, meeting up physically with the team members and brainstorming to come up with what you are holding in your hand was quite exciting and refreshing. It would be an opportune moment to thank all the team members who made this happen.

On behalf of the team, I would also like to thank Dr. Anju Kaicker and Dr. Shalini Sen for being our constant guides, almost acting like a beacon of light.

Although we are sure there is always room for improvement, we expect the next team to make mistakes and learn from them, just as we did, yet carry on this legacy. We truly hope that this effort of ours will not only be informative but will bring a smile to the readers' faces as they go through it.

Happy reading!

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# Expressions 2022




1961 - 2021

Tirumala Tirupati Devasthanams

**Sri Venkateswara College**

(University of Delhi)

Catalysis

The Biochemical Society

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# Catalysis

## THE BIOCHEMICAL SOCIETY

With the aim to ignite a creative spark and hone the literary skills of the students, CATALYSIS, the Biochemical Society of Sri Venkateswara College was established in the year 2004. The Society aims to enhance scientific awareness among the young biochemists while presenting a platform for them to capture their ideas on paper as well as murals. Through Catalysis, the students get to express, explore and experience the joys of science. There are a variety of programs undertaken annually under the aegis of catalysis.

One of the highlights of Catalysis is the departmental magazine, EXPRESSIONS. Every year a theme is chosen, new developments and advancements related to this theme are presented in an interesting and even humorous manner. The students are encouraged to showcase their skills by writing articles, making illustrations or even cartoons that revolve around the chosen topic. The department also invites students and teachers alike to participate in a theme-based photography competition every year, the results of which are displayed in the magazine.

With an eye to foster the habit of trouble-solving and enhancing analytical skills, Catalysis launched AMALGAM, a quiz contest that helps in sharpening agile minds, for the first time in the year 2010. The quiz is multi-disciplinary in nature which enables the participants to develop a holistic thought process to get to the right answer.

MINDSPAR is yet another event organized by the society that is a remarkable platform for ideation and creative thinking on current topics and promotes entrepreneurship. It is organized in 3 different tiers catering to High school, Undergraduate and Postgraduate students in the Delhi-NCR region.

Catalysis organizes insightful and informative lectures by renowned scientists to enthuse the young minds with their scientific journeys. The alumni, who are the pride of the department, are invited to interact with the existing batches of students to provide career counselling. In a nutshell, Catalysis endeavours to provide an environment that fosters 360 degrees growth of its members.

# Core Team 2021-22

## Organizing Committee

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# From the Principal's Desk

## PROF. C. SHEELA REDDY



I am glad to note that the Department of Biochemistry is ready to release its magazine "Expressions" which this year is having 'Epigenetics' as the theme. This upcoming field of research has gained a lot of importance in the last decade and more so now when we all are trying to cope with the Covid-19 pandemic and its after-effects.
Today more than ever, we realise the importance of nutrition, adequate sleep, physical exercise, social interaction and environment in general as well. Research in the field of epigenetics is showing the correlates between lifestyle choices and the expression of genes and their combined effect on disease manifestation. The Department earlier had arranged a two day workshop "Synergise" on 28th & 29th January 2022 to highlight the importance of lifestyle management.

It is heartening to see that the editorial board of the magazine got an opportunity to interview Dr. Sanjeev Galande, Dean of the School of Natural Sciences, who has expertise in the field of epigenetics. I am sure his research experience and words of wisdom must have shed light on some unanswered questions and motivated the students. I take this opportunity to thank Dr. Galande for taking out time for the interview, accepting our invitation to release the magazine and delivering keynote address on 14th March, the day of the Department festival.

I congratulate the entire team for compiling the magazine, which showcases the creativity of the students and their ability to work as a team. I wish the entire Biochemical Society success in their activities.

C. Sheela Reddy
PRINCIPAL

# University of Delhi
# Department of Biochemistry



## From the Department Head's Desk

**PROF. ALO NAG**

I am glad to note that the Biochemical Society of the Department of Biochemistry of Sri Venkateswara College is releasing yet another edition of their annual magazine on "Epigenetics". It is a promising area of research that has taken the center stage after witnessing a decade of research. Epigenetic studies offer a better understanding of the mysteries of many complex diseases. With the advent of high-throughput technologies, the potential and applications of epigenetics have diversified and hence this seems to be a much needed exercise that will refresh and update our knowledge of this rapidly expanding field. I am sure the interaction with the renowned scientist, Dr. Sanjeev Galande will shed light on many unanswered queries and motivate the young minds of the students.

I sincerely appreciate and congratulate the entire team of enthusiastic teachers, staff and students for their tireless efforts and dedication.

My best wishes for the success of the Expression 2022 magazine!

# Interview with



# DR. SANJEEV GALANDE

Currently the Dean of the School of Natural Sciences and the HoD of Life Sciences at Shiv Nadar University, Dr. Sanjeev Galande earlier was the Professor of Biology and Dean of Research & Development at IISER-Pune. There, he led the Centre of Excellence in Epigenetics (CoEE) that studied epigenetic mechanisms and their role in a variety of biological functions.

In 1996, Dr. Galande obtained his Ph.D. in Biochemistry from the Indian Institute of Science. He was a postdoctoral fellow at the Lawrence Berkeley National Laboratory, USA from 1996-2001, where he studied the role of MAR-binding proteins in tumorigenesis.

# INSIGHTS FROM THE INTERVIEW

**Q** What did you aspire to be as a child? Was it being a scientist or something else?

**A** I hope you can deal with very honest answers because those are the answers that you might not be actually expecting or wanting to hear. So the honest answer to this question is that I actually wanted to become a sportsperson. I really tried to engage myself in different kinds of sports, mostly outdoors. I was not much into indoor sports. I am very happy that I spent my life like that. Something totally different actually happened in college that led to an interest in life sciences and that's why I am here now. Otherwise, you would have seen me as a sportsperson.

**Q** But are you still retaining your enthusiasm for sports?

**A** Yes, absolutely!

**Q** So which sports are you keen on?

**A** When one is younger, one likes to try out many things. I used to mostly play games like soccer, baseball, hockey, and to a certain extent volleyball. I would say hockey had my interest for the longest time. But I used to play some Indian sports like Kho-Kho also. In school I was in the Kho-Kho team, in college I was in the soccer and hockey teams and then in senior college, I was in the team for weightlifting. So I've dabbled in all of these things. I think sports builds character, it maintains your health among so many other things. Your profession could be different, but I think sports should definitely be a part of life.

**Q** You did your post-doctoral studies on the role of MAR-binding proteins in tumorigenesis. What interested you in the field of epigenetics and what would you say was the most challenging endeavour amongst all of your projects?

**A** During my PhD studies at IISc Bangalore, I was looking at the chemical mechanism of the topology of chromosomes, and how they segregate. That was my early exposure to some aspects of epigenetics, or I'd say chromatin biology since at that time epigenetics and its tools were not so common; this was during the 90s. That was when I realized that I wanted to learn more about chromosomes, how they replicate and function. Chromatin undergoes compaction and decompaction (the way it happens when we fold clothes). Back then, I did not realize how elegant this mechanism would be, because nobody had the tools to understand it. How, when and where were the questions that remained to be answered. I was very lucky to be a part of this process as it unfolded in the last 3 decades and I've seen how it has evolved, how scientists devised tools to understand this process in its entirety. Chromatin and its smallest unit is involved in compaction. Genes undergo this cycle of decompaction that happens all the time in the cells and enables the cell to switch genes on and off. When I was looking for my post-doctoral program, I knew that this is the area I would like to work on.

Incidentally, a fellowship related to breast cancer was available and my research was based on MAR binding proteins.

**Q** Why did you choose research as a career option over a more lucrative job in the industry?

**A** Here, I would like to latch on to the word lucrative. So for me, excitement is the stuff that actually drove me towards science. Money is not necessarily everything and gone are the days when scientists were considered very poor and not able to afford a decent lifestyle. Right now, they are reasonably well paid. Of course, it cannot match the standards of the industry because they operate on the principle of profitability. A couple of decades ago, working in the industry and working in academia was considered to be mutually exclusive. But now we have a lot of collaborative programs and contract research programs between institutions, universities and industries. I believe research can only advance with the crosstalk between industries as well as academia. The reason why western countries have achieved so much technologically is precisely due to this connection. There are so many opportunities now which have actually blurred the line between these two which used to be watertight compartments up until 10 years ago. You have been witness to the amount of R&D that our industries have done in the last 2 years due to the pandemic. Many new vaccines were discovered and R&D was done indigenously and yielded results within a short span of 1 year! So this is a very good example of the industry and academia being hand-in-glove.

**Q** Have you ever had a Eureka moment?

Which has been your most surprising finding?

**A** Interesting question! There have been multiple eureka moments and these are the moments that keep me going. So far there has not been a single day in my professional life where I have been too bored to go to work. Every day there's this excitement that "Okay, today could be my eureka moment!". So, it need not be once in your lifetime. One such discovery that I can tell you about is something which happened very recently. This actually happened when we were able to show the molecular mechanism of a genetic defect that is known to occur in humans. It's called a 'cleft palate'. There is a bifurcated palate all the way inside the mouth and it has to be rectified using surgical methods that happens because of a developmental defect, very early in life when the embryo is just a few cells old. While we were not working on this, in a serendipitous manner, we were actually able to find the molecular and cellular mechanism of this particular defect. It's a genetic defect and we could actually find the precise epigenetic mechanism of this genetic defect using a model system. Since you can't induce a cleft palate in a human due to ethical reasons, you can only do retrospective research. However, you can use animal models to do this. We were actually able to recapitulate this genetic defect in the zebrafish model. We genetically created the same mutation in zebrafish. While studying the mutant, the entire scan was being developed on the computer screen. The scan was developed and the entire picture was stitched together, we could actually see that the bones in the jaw and the lower jaw of the fish also had this septum which was not fused, and I jumped out

of my seat! When you see this happening that's the proof of the pudding!! That was really the eureka moment.

**Q** You led the team at the Center of Excellence in Epigenetics at IISER, Pune. We were curious as to what led to the establishment of the center by the university. Also, how would you describe your experience working there as a team leader?

**A** This takes me back to several years ago. The origin of the CoE was sometime in 2008. I started my independent lab in Pune in NCCS in the year 2001. For the first 6-7 years there were many projects that we undertook and many of those yielded some very significant yields. During that entire time, I was also working with a set of collaborators within and outside of NCCS. We used to meet constantly and bounce ideas off of each other. I had a whole bunch of collaborators then by 2008. In one such conference, we got together and we thought, why not establish a program where we actually jointly address some of the critical issues, critical problems in epigenetics, and have everyone contribute to this exercise. So we thought of putting this as a program and fortunately, the Department of Biotechnology was promoting the establishment of "Centres of Excellence". This was a grant that the DBT gave us since it was a collaborative exercise, their only condition. We went berserk! Since this involved 6 people across 4 different institutions, we projected using 6 different model systems. It took about one and a half years for us to convince them that this is doable, and then finally by the end of 2009, we got a formal sanction. That was the time I actually moved from NCCS to IISER, Pune.

**Q** I believe you have a similar Centre of Excellence here also at the Shiv Nadar University?

**A** DBT does not have any more of the Centres of Excellence programs, so we could not have Phase-3 funded through DBT. That funding now comes from the Shiv Nadar Foundation so the third phase of Centre of Excellence is going to be at the Shiv Nadar University.

**Q** One of the basic models of molecular biology which is taught in schools is the central dogma. Can you explain how our emerging understanding of epigenetics is changing this model?

**A** The central dogma talks about how genetic information flows through an intermediate which is RNA and RNA is then translated into proteins which are the workers of the cell. That is the basic tenet of the central dogma. Now, of course, there are deviations that were found in the 70s, and that's what taught us about the reverse transcriptases which basically can reverse this flow of genetic information from RNA to DNA. If you're restricted to genetics, the huge amount of complexity that exists in nature cannot be explained. That is actually because of the epigenetic regulation of genes. And that is in form of alternative splicing, post-translational modifications, all of which is like adding different spices to a recipe. Genes are basically being reshuffled in different ways and being given different flavours so that they can actually perform different functions. All of these permutations and combinations of functions are possible because of these various spicy additions because of the epigenetic and post-translational modifications.

**Q** What is it that constitutes a signal? What are the triggers which lead to these epigenetic manifestations?

**A** The triggers could be both external as well as internal. Many times these triggers are through a change in the physical environment – temperature could be a trigger or change in the type of the food could be a trigger. But there are many internal triggers also and those are in the form of hormonal secretions that can change your mood, for example. It alters your genetic circuitry in such a way that different genes are expressed at different times of the day, in different parts of the body which brings the ultimate outcome in form of a change of your behaviour, change of your bodily patterns.

All of this is dependent upon this interplay and that's why it is a complex thing because you are continuously looking at multiple external and internal factors. That's why the answer is not always simple. You cannot pinpoint a single molecule or a single mechanism, it's all interconnected in the body.

**Q** Do twin studies really help in this?

**A** Twin studies also help in this since they serve as a very good control because there the genetic part is almost nullified, there are no genetic differences. So whatever changes you see are because of non-genetic factors.

**Q** To what extent can these epigenetic changes be inherited in the next generation?

**A** It is a very complex question but as I said, technology has evolved for us to be able to quantitatively, as well as qualitatively understand the extent of transgenerational epigenetic transmission. And you'll be surprised that there is a lot of it that is actually transmitted. The bottom line is, we pass on farmore than our genetic content to the next generation. Even aspects like fear, anxiety, mental health can be epigenetically transmitted to the next generation.

As a part of the CoE program, we collaborated with a neuroscientist from TIFR, Professor Vidita Vaidya. She undertook some of the behavioral epigenetic studies and we looked at the molecular mechanisms and saw that in a mouse model, pups of stressed or anxious mothers actually also become stressed and anxious. But unlike genetic disorders, there is a silver lining in epigenetics — epigenetic changes are reversible, genetic changes are not. For example, if a child has sickle cell anaemia, there is nothing you can do unless, of course, you perform gene therapy. But if we have an epigenetic change, that can be reversed.

In mice, if you give antidepressants, Prozac-like molecules, to the pups, you actually see reversible changes in brain circuitry. The genes we tested actually showed reversible epigenetic changes on the upstream regulatory genes. You are basically changing the epigenetic wiring and therefore you see a change in the mental health situation and that is how antidepressants work - by actually rewiring the epigenetic circuitry in the brain.

The same thing can be reversed even by behavioural changes. So for example, if these anxious pups get more parental care, the same molecular changes are seen as you see with the antidepressant treatments. It's amazing to

see that even fear, something so subjective and difficult to quantify, can be transmitted to the next generation. This is not just through DNA and protein modification, but also by the deposition of a new set of RNA molecules, called microRNAs. This is an epigenetic mechanism now - the third epigenetic mechanism. The first one is DNA modification, which is imprinting. Then there are protein modifications, which are the chromatin modifications, and the third one is through RNA and this third part is physically deposited. There is experimental evidence to show how stressed fathers or fathers who have gone through a fear-change paradigm can pass that on to the next generation. In the sperms of these individuals, they found microRNAs were found to have been deposited which caused fearful behaviour in the pups. You experimentally add the same thing in the sperms without the fear, and you can induce fear in the next generation. The kind of sophistication that is coming to experimentation is mind-boggling!

**Q** What is the future of epigenetic therapy in humans?

**A** The future is very bright and there are already many molecules that are in clinical trials. A huge amount of R&D is going on in several companies for discovering the molecules that can epigenetically modulate even the function of the brain, for modulation of depression, anxiety, stress, fear, there are molecules that are being tried.

**Q** What has also interested us is the organization which you are running and so could you tell us about ARBUZA, the company you founded along with Prachi Pandit and Dr. Francois Iris? What is it that you exactly do and what was your aim behind this initiative?

**A** ARBUZA is a lifestyle-based behaviour change program. The collaborators use our knowledge base to create personalized therapy for many of the lifestyle disorders, that is the overall aim of this company. So, so far, we have been able to make some difference to a few individuals and now we are trying to make it bigger for larger organizations, serving either children or other career professionals.

**Q** As a researcher and professor, what is that something you would advise or recommend to us as students interested in the field of research to do outside the standard learning we do as a part of our curriculum?

**A** I just tell people to follow their nose — whatever you like, keep doing that and you will find your way.



# ROLE OF EPIGENETICS IN ALLERGIES

NANDIKA SANJOG SAHANI
B.Sc. (Hons.) Biochemistry, III year

An allergy is an exaggerated immune response generated by the immune system. It is “exaggerated” since these substances may not produce such a response in non-allergic individuals. Substances that generate an allergic response are called “allergens” and these include pollen allergens, insect allergens and food allergens among others. When a person who is sensitized against a particular allergen comes in contact with it again, the immune system tends to develop a response through the IgE antibody. People who are prone to displaying a reaction against allergens are known as “allergic” or “atopic”. Many such substances often stay hidden from our knowledge which is why it becomes difficult to detect an allergy. Over the years, many scientists and researchers have studied the influence of genetics on allergies but in the last decade, studies on epigenetics and its role in allergy is being studied. Epigenetics is a study that explains heritable phenotypic changes which do not involve alterations in the DNA sequence. [1,2,3]

In earlier times, many scientists and researchers have conducted studies so as to understand the role of genetics in allergies, and it was found that there could be multiple reasons for an individual to develop an allergy, and these could be influenced by the environment that an individual has been exposed to. This observation led to the onset of studies that explained how epigenetic changes can be responsible for allergies. After various studies and experiments conducted all over the world, it was deduced that epigenetic changes do play a major role in allergic reactions too! It has now been widely accepted that lifestyle changes and environmental changes play a major role in increasing the incidence of allergies. Extensive research projects are going on in order to understand the various epigenetic mechanisms in the field of allergies. This in turn has shed light on numerous aspects that have remained undiscovered till now. Many studies which are being conducted focus on how the epigenetic signatures (such as DNA methylation), can be used as potential biomarkers, so as to detect allergies in patients. [3]

However, in order to understand the cellular and molecular mechanisms of how environmental changes actually influences allergies, it is important to understand epigenetic modifications, which would highly help us understand the high degree of plasticity observed among immune responses throughout life. One such role of epigenetics is in the expression of genes related to the release of cytokines by mature T-cells. This process is highly controlled by epigenetic modifications. Here, DNA methylation patterns play a major role in influencing gene expression. For instance, it has been widely known that epigenetic modifications either favour the transcription of specific genes or inhibit the same.

DNA methylation is known to silence the genes, thus inhibiting transcription. The same pattern takes place during the maturation of T-cells. In a

study, it was found that the genes specific for the maturation of Th1 remained demethylated during the maturation phase, whereas the one essential for the maturation of Th2 cells stayed methylated. This gives us an insight into how epigenetic modifications can influence the mechanism of T-cell maturation, which plays a major role in allergic reactions.[3, 4]

Pollen grains are well-known environmental factors that influence allergic patterns. During the pollen season, methylation patterns were found to be directly linked with the severity of allergic reactions in patients. An additional study has also revealed that pollutants (especially air pollutants) are connected to an increase in allergic reactions in susceptible individuals, and epigenetic mechanisms are believed to play a part in this process. There has been a significant increase in DNA methylation at CpG sites of the FOXP3 locus of Treg cells, which has been further associated with the increase in exposure to polycyclic hydrocarbons and the development of allergy. Further, children with high levels of FOXP3 DNA methylation have also been found to have an increased risk of asthma and chronic wheezing.[5]

In studies across the world, it was also found that living and environmental conditions to which an individual has been exposed also play a major role in allergy development. For example, the hygiene hypothesis states that early-life microbial exposure that is proportional to the number of children in a household protects against the development of allergy diseases. It also states that the changes in lifestyle along with advances in sanitation and public health has contributed towards the rise in the incidence of allergies over the last few decades. In the absence of infection, however, exposure to microbes or their structural elements found in diverse indoor or outdoor environments can occur. Such microbial chemicals, which are identified by the innate immune system, can also cause chronic inflammation, which can lead to the formation of anti-inflammatory protection. This has been shown for atopic illnesses as well, particularly in studies on the influence of farming on allergic propensity. These studies have found that children who are exposed to microbiota found in farming/rural contexts early in life develop fewer allergies than their inner-city counterparts.[4]

It was also found that environmental modifiers (positive as well as negative) play a major role in explaining the adverse prevalence of allergic disorders. These modifiers have the potential to not only modify genetic proneness but also to completely eradicate the same, for example, a person with a genetic inclination to bee allergy who lives on an island devoid of Hymenoptera will never acquire atopic sensitization and the resulting allergic symptoms. The epigenetic influence is quite interesting, however, the many facets associated with them need to be researched.

References:

1. Krishna, M. T., Mahesh, P. A., Vedanthan, P. K., Mehta, V., Moitra, S., & Christopher, D. J. (2020). The burden of allergic diseases in the Indian subcontinent: barriers and challenges. The Lancet. Global health, 8(4), e478–e479. https://doi.org/10.1016/S2214-109X(20)30061-9
2. Bhattacharya K, Sircar G, Dasgupta A, Gupta Bhattacharya S: Spectrum of Allergens and Allergen Biology in India. Int Arch Allergy Immunol 2018;177:219-237. doi: 10.1159/000490805
3. Potaczek, D. P., Harb, H., Michel, S., Alhamwe, B. A., Renz, H., & Tost, J. (2017). Epigenetics and allergy: from basic mechanisms to clinical applications. Epigenomics, 9(4), 539–571. https://doi.org/10.2217/epi-2016-0162
4. Venarske, D., & deShazo, R. D. (2003). Molecular mechanisms of allergic disease. Southern medical journal, 96(11), 1049–1054
5. DeVries, A., & Vercelli, D. (2015). Epigenetics in allergic diseases. Current opinion in pediatrics, 27(6), 719–723. https://doi.org/10.1097/MOP.0000000000000285

# the epigenetic clock



ANANYA BANDYOPADHYAY
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We all know age is a known factor associated with an increased risk for chronic diseases and impairment in physiological functions of the systems of the body in general. However, it is not necessary for 2 individuals of the same "chronological" age to show similar age-related health conditions since that depends on their "biological" or "physiological" age instead. We can define chronological age as the time from birth till the present while biological age is associated with biological functioning, which will vary due to multiple lifestyle factors. [1]

Right from birth, developmental changes lead to age-associated changes in gene expression, growth, and physiology. [5] One of these changes is the epigenetic modifications to the genome — reversible modifications of DNA and chromatin structure that mediate the interaction of the genome with a variety of environmental factors to generate changes in the patterns of gene expression in response to these factors and that are potentially transmittable to daughter cells.

Epigenetic changes can occur through a variety of mechanisms, the most common and important one being DNA methylation, or the addition of a methyl (-CH3) group to the cytosine residues in what are known as CpG islands, or dinucleotide CG repeats.

For over many years now, epigenetic patterns have been studied to find correlations between the ageing process and degree of methylation, and it is only recently that it is being used as a biological marker to determine the age — biological age — of individuals.

In order to be able to reduce the risk of diseases associated with ageing, the most important thing is to identify the causal factors, their associated pathologies, and the underlying physiological changes. That would require quantification and characterisation of biological ageing with the use of appropriate biomarkers, which in itself is an extremely daunting task because even to date, a lot is unknown, primarily because the process itself can be a result of completely unrelated factors and so very typical of an individual. [4]

And that is where the concept of epigenetic clocks comes into the picture.

The basic methodology adopted to develop these epigenetic clocks is to measure DNA methylation in biological samples and find gene markers that show a high degree of methylation-age relationship. Because the parameter being measured here is DNA methylation, epigenetic clocks are more

accurately termed as “DNAm age estimators”. These sets of CpGs are then coupled with mathematical algorithms to estimate the age (in units of years) of a DNA source, such as cells, tissues, or organs. [6]

The first two epigenetic clocks were reported in 2013 and both measured the rate of ageing of biological samples but were not found to be very accurate for the paediatric population, most probably due to the continuous changes occurring during the developmental process. [2]

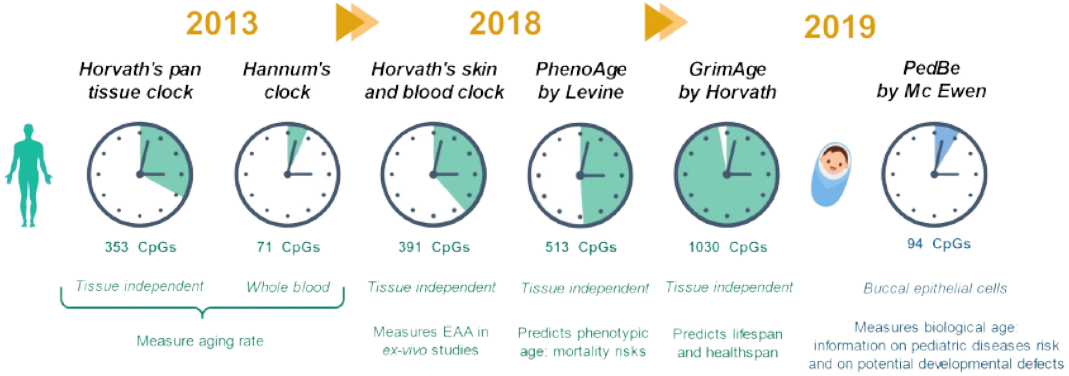



Figure 1 Wandering along the epigenetic timeline (Topart, C., Werner, E. & Arimondo, P.B.)
EAA: epigenetic age acceleration

However, the latest epigenetic clock PedBE, developed by Mc Ewen in 2019, is more accurately able to determine the biological age in the paediatric age range. [1]

One might wonder why there is such an interest in knowing the biological age. It is pretty straightforward: we wish to predict the risk of developing diseases, assess the mechanisms underlying the process of ageing, develop interventions to delay ageing-associated declines in health, and in the case of the younger populations, study and predict any potential developmental challenges.

References:


1. Topart, C., Werner, E., & Arimondo, P. B. (2020). Wandering along the epigenetic timeline. Clinical epigenetics, 12(1), 97. https://doi.org/10.1186/s13148-020-00893-7
2. McEwen, L. M., O'Donnell, K. J., McGill, M. G., Edgar, R. D., Jones, M. J., MacIsaac, J. L., Lin, D., Ramadori, K., Morin, A., Gladish, N., Garg, E., Unternaehrer, E., Pokhvisneva, I., Karnani, N., Kee, M., Klengel, T., Adler, N. E., Barr, R. G., Letourneau, N., Giesbrecht, G. F., ... Kobor, M. S. (2020). The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells. Proceedings of the National Academy of Sciences of the United States of America, 117(38), 23329–23335. https://doi.org/10.1073/pnas.1820843116
3. Grodstein, F., Lemos, B., Yu, L., Iatrou, A., De Jager, P. L., & Bennett, D. A. (2021). Characteristics of Epigenetic Clocks Across Blood and Brain Tissue in Older Women and Men. Frontiers in neuroscience, 14, 555307. https://doi.org/10.3389/fnins.2020.555307
4. Oblak, L., van der Zaag, J., Higgins-Chen, A. T., Levine, M. E., & Boks, M. P. (2021). A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing research reviews, 69, 101348. https://doi.org/10.1016/j.arr.2021.101348
5. Jones, M. J., Goodman, S. J., & Kobor, M. S. (2015). DNA methylation and healthy human aging. Aging cell, 14(6), 924–932. https://doi.org/10.1111/acel.12349
6. Horvath, S., & Raj, K. (2018). DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nature reviews. Genetics, 19(6), 371–384. https://doi.org/10.1038/s41576-018-0004-3


Epigenetic changes made under stressful conditions will revert over time if environmental stressors are removed

# CAN WE INHERIT TRAUMA?

PARUL YADAV
B.Sc. (Hons.) Biochemistry, I year

"Your genetics load the gun, your lifestyle pulls the trigger."
-Mehmet Oz

We all are leading assiduous, tied-up lifestyles nowadays. Human existence is a race and each one of us is running to achieve some goals. Whom are we competing with? In such taxing times with much of the world under the grip of anxiety and hardship, trauma easily finds its way into one's life. And it may impact our future offspring. The genes which we transfer to our upcoming generations shape their lives, but new research is revealing that our adversities and hardships can also leave their mark on them.[1]

Sounds weird.....right? But I must tell you that a growing body of research suggests that trauma can affect posterity.

Here's how: According to research trauma affects the chemistry of our genes, which can be passed to our descendants. It does not cause any mutations in our genetic codes but it creates a disturbance in the expression of gene mechanisms. This alternation is not Genetic but EPIGENETIC.

Epigenetics controls how and why our genes are expressed.



*Credit: Alamy/Getty images/BBC*

A couple of examples from the past evidently show that it might be possible to inherit a parent's trauma.[2][3]

Like, there are reports of the Dutch Hunger Winter, a period of famine towards the end of World War II. During that period Nazis blocked the food supply in the country due to which much of the Netherlands starved to death. But pregnant women were particularly vulnerable and unborn children in their wombs were majorly affected for the rest of their lives.[4] Scientists found that those who had been in the uterus during the famine were heavier than other infants because their mothers while starving automatically silenced the gene in their unborn children involved in burning body fat. So, when they reached middle age, they had higher LDL cholesterol and triglyceride levels. Consequently, they suffered higher rates of obesity, diabetes and schizophrenia.[5][7]

Another study in 2018 showed that the Civil War soldiers who spent most of their time in prison had a negative impact on their offspring. Their male offspring were more likely to die early (after the age of 45) than those whose fathers were not prisoners during the war. This excess mortality was mainly due to higher rates of a cerebral haemorrhage. [6][7] Researchers concluded that parental stress could affect future generations adversely because childhood trauma impacts children to different extents. And that impact may occur through epigenetic channels.

Despite the fact that epigenetic studies have proved its concept of inheritance of trauma in the past, a few scientists don't agree with that. This field of science is still new and is still finding its way forward. Investigators in the field say that pieces of evidence are premature.
"The effects we have found have been small but remarkably consistent and significant", said Moshe Szyf, a professor of pharmacology at McGill University.

Much of this research is incredibly compelling, but until more studies are done on the intergenerational effects of trauma, we have to wait to tease out all the possible implications. Could the current COVID-19 pandemic and extreme stress it is causing the world cause epigenetic changes to offspring? It's possible, but only time will tell.



*Source: Athleticlab.com*

References:
1. Henriques, M. (2019). Can the legacy of trauma be passed down the generations? Bbc.com. https://www.bbc.com/future/article/20190326-what-is-epigenetics
2. Can We Really Inherit Trauma? (Published 2018). (2022). The New York Times. https://www.nytimes.com/2018/12/10/health/mind-epigenetics-genes.html
3. https://www.facebook.com/verywell. (2012). How Does Intergenerational Trauma Work? Verywell Health. https://www.verywellhealth.com/intergenerational-trauma-5191638#citation-1
4. The Famine Ended 70 Years Ago, but Dutch Genes Still Bear Scars (Published 2018). (2022). The New York Times. https://www.nytimes.com/2018/01/31/science/dutch-famine-genes.html
5. Schulz L. C. (2010). The Dutch Hunger Winter and the developmental origins of health and disease. Proceedings of the National Academy of Sciences of the United States of America, 107(39), 16757–16758. https://doi.org/10.1073/pnas.1012911107
6. Baggaley, K. (2018, November 9). Civil War study shows father's stress affects son's lifespan. NBC News; NBC News. https://www.nbcnews.com/mach/science/civil-war-pow-study-finds-father-s-stress-can-alter-ncna934546
7. Khazan, O. (2018, October 16). The Atlantic. The Atlantic; theatlantic. https://www.theatlantic.com/health/archive/2018/10/trauma-inherited-generations/573055/

> Metastable epialleles are alleles that are variably expressed in genetically identical individuals due to epigenetic modifications established during early development

# Identical twins...or not?

REA PASRICHA
B.Sc. (Hons.) Biochemistry, II Year

Most of us know at least one pair of identical twins. In fact, we might even have been confused between the two of them for a while (have you ever been pranked by twins?), and as we gradually got to know them more, we understood the differences which made them unique individuals. Twins being dressed in the same clothes and having the same hairstyles is something common to every part of the world. Even in movies and television shows, it is not unusual to see a pair of twins portraying the same character, which goes unnoticed due to the fact that they have identical DNA sequences.



Emma Geller-Green was portrayed by identical twins — Cali and Noelle Sheldon in the show Friends.
Source: www.looper.com

Despite all the similarities, identical twins are not exactly identical. So, what is that thing which makes them different? One of the answers is: Epigenetics. The word literally means 'on top of genetics'. It includes those modifications which do not essentially change the actual DNA sequence but change the ways in which the genes are 'read', hence producing different phenotypic effects. Epigenetic modifications can be of different types, including the addition of methyl groups, histone modifications, etc. Since twins are also two separate human beings, many things in their lives are bound to be different, and this can begin right at the beginning of their lives i.e., in the womb itself. Some examples of differences amongst twins are: monozygotic twins sharing a placenta and one twin having a more advantageous connection to the placenta hence receiving more nutrients than its twin; one twin moving to a small town while the other to a big city. It is the environmental differences like these that cause changes in the epigenome. Monozygotic twins have therefore been studied extensively to understand the role of 'nurture' (as the 'nature' component is a constant for them) in humans and its effects on diseases and behaviours. [1]

Dr. Nancy Segal, Director of the Twin Studies Center, and a Professor of Psychology at California State University, Fullerton has played a role in conducting multiple twin studies. One of the studies she was part of, was on two sets of brothers in Colombia who were monozygotic twins, switched at birth.

Epigenetic comparisons of both sets of twins were carried out using cheek-swab samples. On reading the methylation patterns, which is a type of epigenetic marking, it was found out that one pair of the identical twins was epigenetically similar (but not identical) while the other pair was significantly different. They hypothesized that these variations were due to the extreme differences in the environments both the twins grew up in.



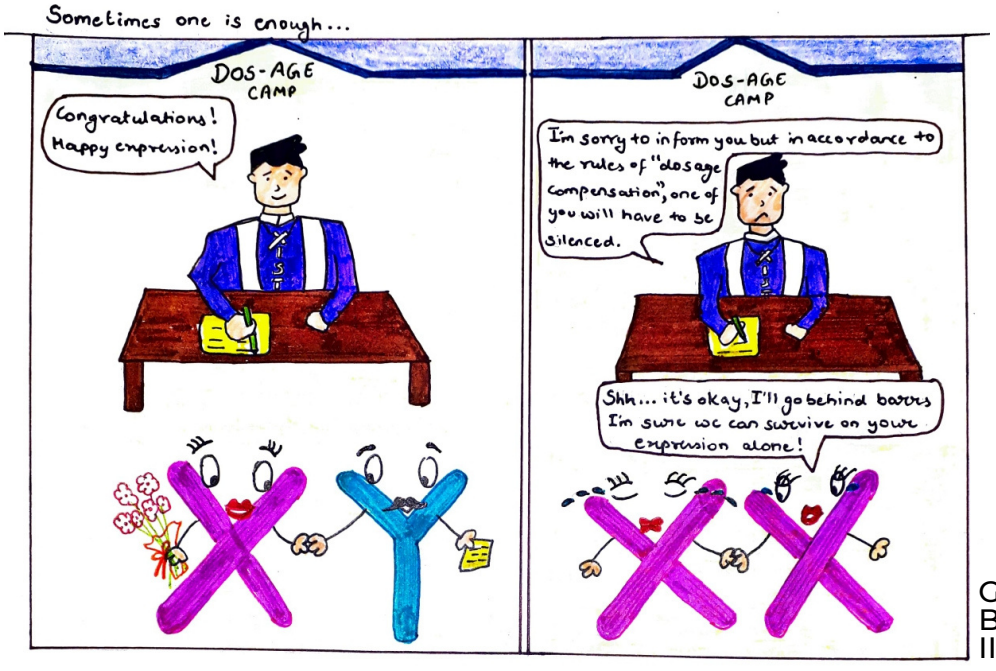
The two sets of Colombian twins who were switched at birth.
Source: www.theatlantic.com

Two of them grew up in the city of Bogotá and the other two, on a remote farm. It was also concluded that the DNA-methylation differences within both reared-apart twins played a role in influencing several genes and genetic pathways. Additionally, one of the two sets of twins, despite being reared-apart, shared similar eating habits, and both the twins of the other pair had been smokers and had a speech impediment. [2] [3]

Similar studies on twins may allow us to expand our knowledge of human behaviour, physical traits, and many diseases, including Rheumatoid Arthritis, PCOS, Type 2 Diabetes, and Cancer, from an epigenetic point of view.

References:


1. Rettner, R. (2013, June 25). Epigenetics: Definition & Examples. Livescience.Com. Retrieved January 4, 2022, from https://www.livescience.com/37703-epigenetics.html
2. Hayasaki, E. (2018, May 17). Identical twins hint at how environments change gene expression. The Atlantic. Retrieved January 11, 2022, from https://www.theatlantic.com/science/archive/2018/05/twin-epigenetics/560189/?utm_source=copy-link&utm_medium=social&utm_campaign=share
3. Segal, N. L., Montoya, Y. S., Loke, Y. J., & Craig, J. M. (2017). Identical twins doubly exchanged at birth: a case report of genetic and environmental influences on the adult epigenome. Epigenomics, 9(1), 5–12. https://doi.org/10.2217/epi-2016-0104



Garima
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III Year

# Inheritance of the subconscious mind

GARIMA
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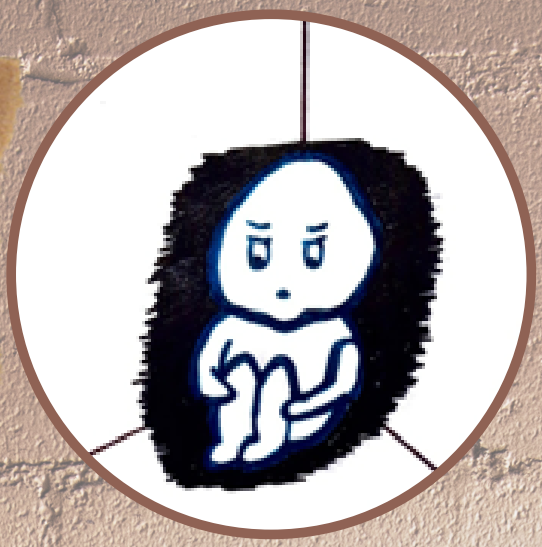


Transgenerational transmission of trauma is the process by which a traumatic episode experienced by a generation is transmitted to the next generation. Strictly speaking, it is when the generation under scrutiny manifests their ancestors' inherited emotional problems, which they have never been exposed to. So, the manifestation of that trauma cannot be attributed to being the direct effect of the traumatic event.[1][2]

For instance, the children of holocaust survivors have nightmares of being trapped, tortured, and undergoing sufferings they've never even encountered. The offspring often suffer from an inability to cope with stress and incapacitating anxiety. They are not seeing the same nightmares i.e., the content of the nightmare is not the same, but the feelings associated with it like that of fear, stress, and terror are the same. It will be manifested in the dreams of the child not as what the parents saw or experienced per se, but as what the child associates those feelings with or what they recognize.[1]

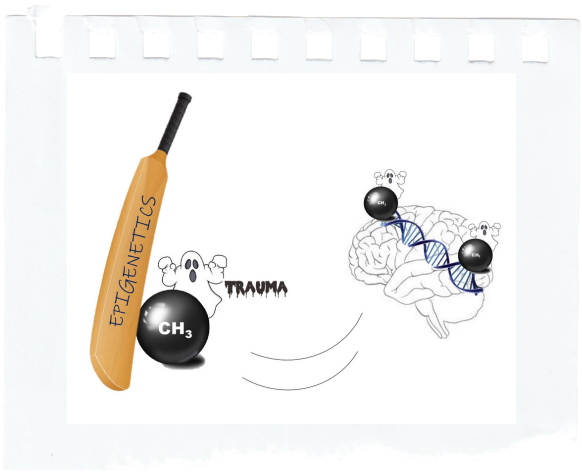
One obvious explanation is that it can be a manifestation of the childrearing capabilities of the parents, who might be suffering from PTSD (Post-traumatic stress disorder), their unconscious fears, the household values, and the opinions of ancestors passed down as knowledge. But even in a relatively "normal domestic environment" or many generations down the line, such stress triggers are still observed in the offspring i.e., the child inherited the psychological trauma despite having a normal enough childhood. [1]

Another reason is that there might be some disorders, like biological stress responses and catalytic triggers, in the parent which are being genetically transferred to the child. There have been studies that infer that there are heritable components in an individual's genome, which makes them susceptible to PTSD. [3] These genetic changes are attributed to epigenetics, inheritable changes in the expression of the genes without any change in the DNA sequences. These epigenetic modifications in gene expression are influenced by environmental stress or significant emotional trauma which leaves a chemical imprint on the genome, which then is passed down to subsequent generations. There are several epigenetic mechanisms like DNA methylation, histone remodelling, transfer of non-coding RNA and RNA modifications& regulations, etc. through which these chemical tags are produced and incorporated into the genome. [1][2]

The epigenetic memory associated with a particular cell can explain how experience is

passed across generations.

“Elements of the collective experience of the species are reflected in the genome, while the experience of the individual is reflected in the expression of that genome.”
-Perry (1999) [4]




There have been several research studies that interlink epigenetic changes in the gene expression of the individual to emotional trauma experienced by the individual’s mother during pregnancy or ancestors. Examples of some such studies are:

- FKBP5 (FK506-binding protein), which is a regulator of glucocorticoid activity, was hyper-methylated at intron 7 in holocaust survivors but lower in their offspring. However, the mechanism has not been established. The authors inferred the reason to be a biological adaptation. [5]
- Mothers exposed to genocide (Rwanda genocide) during gestation, as well as their children, were found to have higher levels of methylation at exon 1F promoter of NR3C1 (nuclear receptor subfamily 3 group C member 1), which is a glucocorticoid receptor gene. Lower levels of cortisol were observed in them relative to non-exposed mothers and children, suggesting that the trauma-induced differential methylation can be transmitted vertically. Low cortisol levels are associated with PTSD.[5]
- Additionally, prenatal maternal stress also correlates with high methylation of NR3C1, and also with the low weight of the newborn. The researchers proposed that increased methylation can lead to constrained gene expression, restricting physiological or psychological stress responses.[5]

Therefore, transgenerational trauma can also cause deterioration in the offspring’s physical health and psychological health.

Certain limitations are often observed in these studies like limited sample size, fragile physical health of survivors during the ordeal leading to lasting complications. Other factors like uniformity in the ethnicity, lifestyle, the socio-economic groups of the individuals under study and geographical area the individuals belong to, etc. also influence the outcomes. [5]

Now, why do we need an improved understanding of epigenetic trauma transmission? It would help in accurate diagnosis of trauma survivors, better preventive measures, to more targeted treatment interventions, by psychological and pharmacological as well as epigenetic therapies. It might help the trauma survivors in claiming compensation for the trauma inflicted since it might affect their future generations. It will shift the perspective of the population towards understanding the impact our psychological health has on our physical health, overall lifestyle, and our future generations.[1]

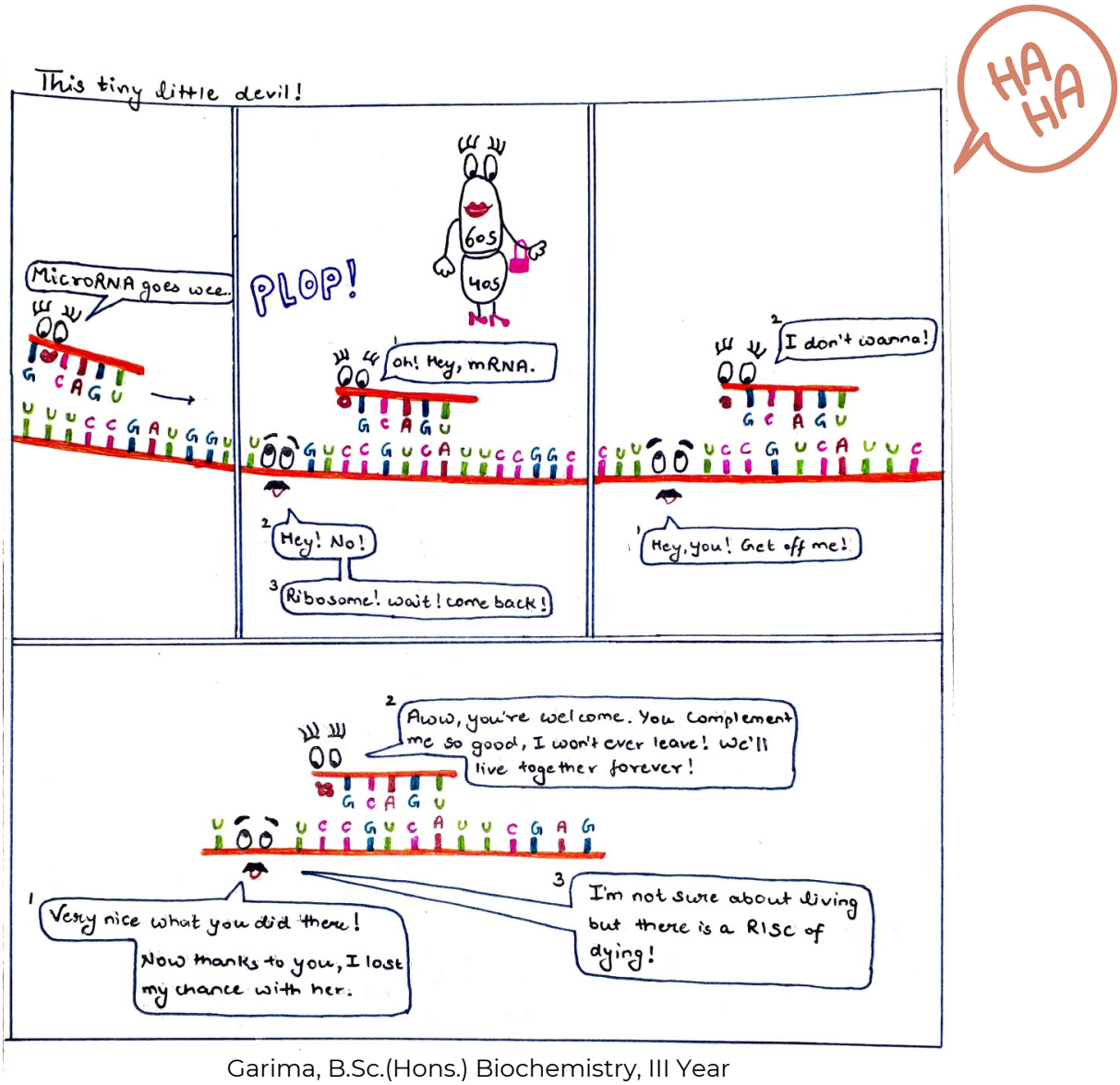
Currently, there is limited literature available with explicit evidence to support the epigenetic transmission of transgenerational trauma, though

we have analyses and research that support this hypothesis. There have been recent advances that may lead to a promising research paradigm in this field.

Epigenetic modifications can influence the experiences passed onto generations. Hence studies in this field can help us understand and handle the trauma experiences better rather than suffering through them without even comprehending the why and the how.


References:

1. Kellermann N. P. (2013). Epigenetic transmission of Holocaust trauma: can nightmares be inherited? The Israel journal of psychiatry and related sciences, 50(1), 33–39.
2. Perez, M. F., & Lehner, B. (2019). Intergenerational and transgenerational epigenetic inheritance in animals. Nature cell biology, 21(2), 143–151. https://doi.org/10.1038/s41556-018-0242-9
3. Skelton, K., Ressler, K. J., Norrholm, S. D., Jovanovic, T., & Bradley-Davino, B. (2012). PTSD and gene variants: new pathways and new thinking. Neuropharmacology, 62(2), 628–637. https://doi.org/10.1016/j.neuropharm.2011.02.013
4. "Splintered Reflections: Images of the Body in Trauma" (Edited by J. Goodwin and R. Attias) Basic Books. URL: http://www.healing-arts.org/tir/perry_memories_of_fear.pdf.
5. Youssef, N. A., Lockwood, L., Su, S., Hao, G., & Rutten, B. (2018). The Effects of Trauma, with or without PTSD, on the Transgenerational DNA Methylation Alterations in Human Offsprings. Brain sciences, 8(5), 83. https://doi.org/10.3390/brainsci8050083


Garima, B.Sc.(Hons.) Biochemistry, III Year

# FOREVER YOUNG

AYESHA MIRZA
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In me she has drowned a young girl, and in me an old woman
Rises toward her day after day, like a terrible fish.
- Sylvia Plath

She got up and walked lethargically towards her day. It is the year 1996, Television is turned on in the background, and the word 'Titanic' comes up. And now our protagonist in her 80s is rushing on the harbour excitedly and narrates the event that happened in 1912, where soon we see a girl of seventeen, lips and cheeks rose-red complementing her name, walking towards the doomed ship majestically. Watching it for the first time in 2008, I had a revelation of how ageing can have a gruesome yet poetic aspect to it.

As an observer, I was satisfied with just the natural process leading towards senescence but now years later, I am pondering over the question "Do individuals age differently?" For a subject like this, there are not one but many answers. Browsing the net, many links were pointing towards genetics as a broad answer to the query but DNA is not the answer to all the attributes we have, sometimes it's the influence from outside that makes us work differently. Huckleberry Finn being the most impelling model in Tom Sawyer's life, shaped his character to a great extent and was the reason behind most of his actions in life even when they parted their ways. Likewise, we may hold epigenetics (meaning 'above genetics') as a culprit to this multifactorial biological process of ageing. Biochemistry shows us how the environment influences genome functions by acting on nucleosomes and their component histones thereby removing the total blame laid squarely on the shoulders of DNA.

Since times immemorial, stress has been an external factor, a result of our habitual activities that had an effect on the physiological slowing down of our cellular machinery, when there is more breakdown than regeneration suddenly it starts to show up on our epithelial cells and the next thing we know, there is a silver lining in our hair, and the creases behind our eyes have become more prominent. The strain is no longer reversible but yet epigenetics is something that is claimed to be a reversible process. Nevertheless, it would be more proper to say that to a certain extent epigenetics is reversible. Will your ageing process differ if one moment you are living a sedentary lifestyle and the next moment you start living like you are under a military schedule? Yes, it might, if we are consistent with the new routine for a considerable period of time.

Let's compare two different lifestyles. On one hand, we consider Helen of Troy, a fictional character who lives her day wandering the castles of Sparta, the daughter of Zeus, pouring her goddess beauty?, and on the other hand, we have Katniss Everdeen from district 12, living as a destitute competing in the hunger games and working different part times just to gain a loaf of bread. So who is going to age faster between the two? Can't deny that Helen didn't have anything to worry about, being very much preoccupied with the battle between her admirers. I will leave the readers to answer the question. However, two people not biologically related and of the same age living under similar conditions may age differently because here our heritable genes play a large role in our body metabolism and how our body responds to the external stimuli. And hence we cannot clearly say "Epigenetics will free us from the tyranny of selfish DNA". However, the discovery of epigenetics in the 2000s has taken a huge responsibility off of our gene's shoulders and may ease it up because 'uneasy lies the head that wears the crown'. Let the monarchy end and democracy walk in. Vive la revolution.

May you build a ladder to the stars
And climb on every rung
May you stay forever young

(Forever young by Bob Dylan, 1966)

# STRESS CAUSING DEPRESSION

From the Epigenetics Perspective

ANANYA CHUGH and KANGNA VERMA
B.Sc. (Hons.) Biochemistry, III year

Depression affects around 280 million people globally, and in its most severe form, it can lead to suicide. Every year, over 7,00,000 people commit suicide, making it the fourth greatest cause of death, especially among those aged 15 to 29 years. [1] According to the definition of depression (major depressive disorder), it's a widespread medical condition that leaves a negative impact on your feelings, thoughts, and actions [2]. Environmental stresses, like childhood trauma, interpersonal conflict, are the most common causes of depression. Indeed, the link between environmental stress and depression has been well established for decades. However, how does this relationship unfold over our lifespan? and how adversity shapes the onset of depression isn't clear. Hence, stress can cause depression but what's the particular biological pathway?

Stress can result in depression via epigenetic changes which are among some of the mechanisms for which increasing evidence is becoming available. In layman's terms, epigenetics is a mechanism for controlling when and how our genes are expressed. Stressors are thought to interact with the genome, causing stable alterations in DNA structure and expression, which could be the cause of disordered behaviour in depressed people. Broadly, epigenetics refers to the processes that affect gene expression and translation and do not involve direct changes in the DNA sequence. DNA methylation (DNAm), small non-coding RNAs such as microRNAs (miRNAs), and histone modifications, are considered as some of the mediators of epigenetic changes.[3]

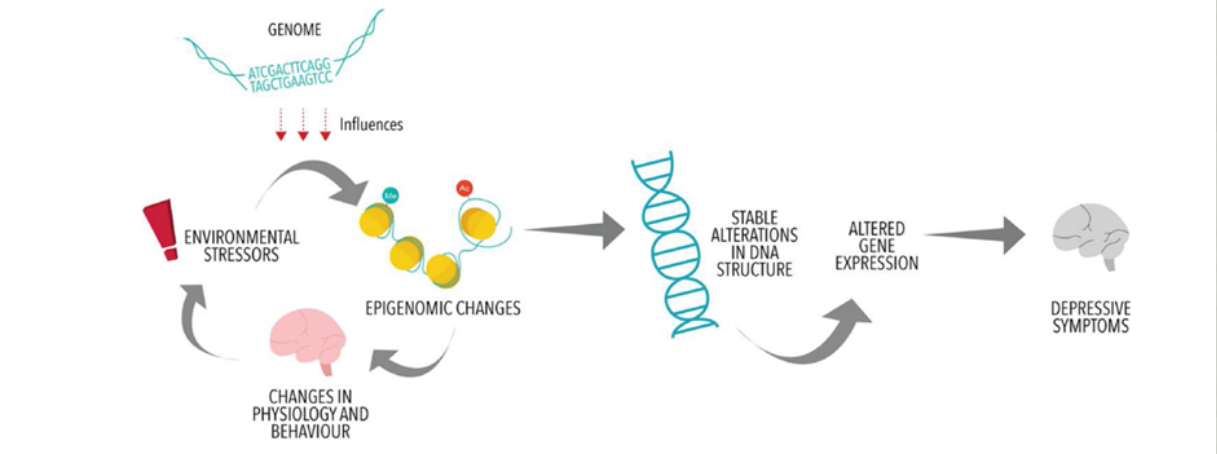



Figure 2: Stress, epigenetics and depression: A systematic review [4]

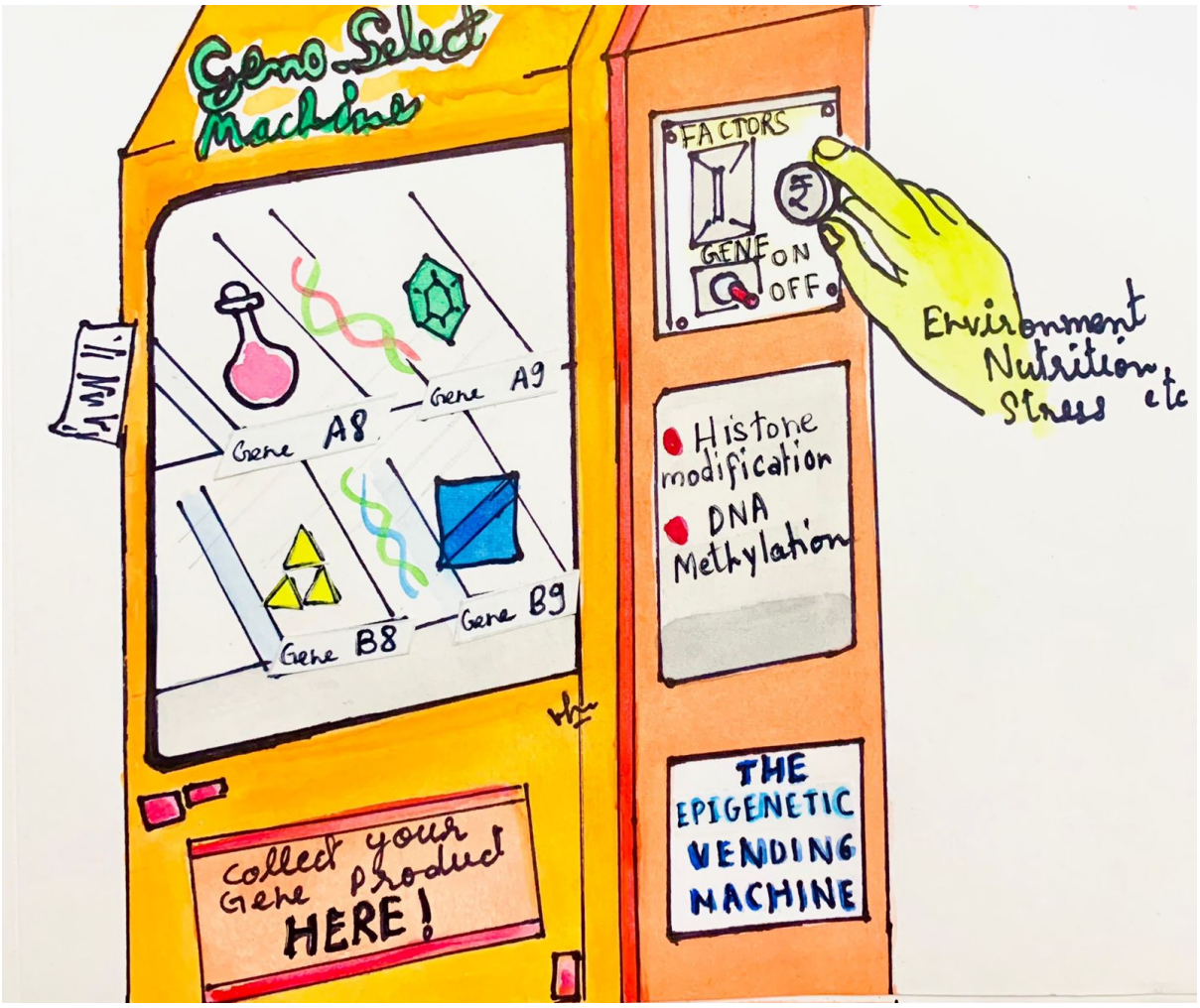
A study by Jakobsson et al. (2008) showed that in the rodent brain, persistent unpredictable stress increased histone acetylation, causing greater anxiety-like behaviour and sensitivity to stress-induced cognitive impairment. Seo et al. (2016) also found that through epigenetic alterations in the hippocampus BDNF gene, rats exposed to early life stress, such as postnatal mother separation, were more vulnerable to stress when they mature. [4] The epigenetic modification of a variety of distinct genes, including NR3C1, SLC6A4, BDNF, FKBP5, SKA2, OXTR, and oligodendrocyte genes LINGO3, POU3F1, and ITGB1, has been examined with respect to stress and depression, according to Park et al.

(2019). Their findings imply that early childhood adversity and environmental stress may affect the epigenetic activity and have long-term effects, such as an increased likelihood of unfavourable mental health outcomes such as Major Depressive Disorder. [4]

To conclude, we don't just inherit our biology we also impact it, which can be both a benefit and a very serious burden. Today we can look for treatments of MDD, by understanding the molecular mechanisms that control it and reversing the negatively impacting epigenetic causes of this disease.

References:

1. Depression. (n.d.). Retrieved January 30, 2022, from https://www.who.int/news-room/fact-sheets/detail/depression
2. American Psychiatric Association
3. Penner-Goeke, S., & Binder, E. B. (2019). Epigenetics and depression. Dialogues in Clinical Neuroscience, 21(4), 397–405. https://doi.org/10.31887/DCNS.2019.21.4/ebinder
4. Park, C., Rosenblat, J. D., Brietzke, E., Pan, Z., Lee, Y., Cao, B., Zuckerman, H., Kalantarova, A., & McIntyre, R. S. (2019). Stress, epigenetics and depression: A systematic review. Neuroscience & Biobehavioral Reviews, 102, 139–152. https://doi.org/10.1016/j.neubiorev.2019.04.010
5. Stress Exposure, DNA Methylation, and Risk for Depression: Dr. Erin Dunn https://www.youtube.com/watch?v=aT6GOQ-lyT8




Vinita Khokhar, B.Sc. (Hons.)
Biochemistry, III Year

# ARE YOU A HORROR MOVIE FANATIC? HERE'S WHAT EPIGENETICS HAS TO SAY...

Horror Movie Fanaticism, Epigenetics and The Dilemma of it being more than just a Harmless Binge-Watching Habit

VINITA KHOKHAR
B.Sc. (Hons.) Biochemistry, III year

Fear is a complex phenomenon that makes an individual equipped to battle survival threats by automatic adjustment of cardiovascular, skeleton-muscular and endocrine functions and psychological processes viz. attention and memory. Genetics is the study of inheritable traits; but Epigenetics is the study of inheritable traits that are NOT caused by changes in the genetic nucleotide (that we fondly remember as A, G, T and C) sequence.

To understand the mechanism of fear, we can take a closer look at the behavioural studies done on bees by Dr. Robinson, a professor of entomology at Illinois. When a honey bee perceives a threat, its neurons rapidly fire to provoke a startling response. However, the bee's brain continues to respond on the molecular level after the threat has subsided to prepare itself for potential future threats with changes in gene expression. Although these changes can take as short as minutes to occur, they are not ephemeral, and can last for hours, days or even longer.

Neuro-imaging studies have revealed that the amygdala is steadily activated during fearful situations. When we decide to stimulate our brains with some horror content on Netflix, a subcortical structure called the amygdala - the emotional centre of the brain, gets triggered and an elevated heart rate and breathing rate is observed. This happens because of a stress signal sent to the hypothalamus from the amygdala; which in turn, stimulates the Sympathetic Nerv-ous System and the adrenal glands release a class of hormones called catecholamines (like Epinephrine) into the bloodstream(1). Simultaneously, activation of the hypothalamus and the hypothalamus-pituitary (HPA) axis leads to a Cortisol surge owing to which the body is plunged into a high alert (high energy) state.

Under normal physiological conditions, the glucocorticoid receptor binds to an Hsp90 chaperone in the cytosol. But steroid hormones, such as Cortisol, are lipophilic and can cross the cytoplasmic membrane to bind to specific receptors in the cytoplasm, such as the glucocorticoid receptor, causing Hsp90 to dissociate. This newly formed cortisol-receptor complex can then easily gain entry into the nucleus and affect the transcription of genes. (2)

In the same chain of events, deliberate and prolonged exposure to stressful environment can lead to a discrete array of epigenetic changes. In a study, 29 percent of test subjects showed that the effects from the exposure to horror in childhood persisted years later and altered normal behaviour such as sleeping and eating while 53 percent of the subject suffered from anxiety and 18 percent from fear of dying. All of these secondary conditions especially sleeplessness have long been shown to be linked with epigenetics, Merely one night of bad sleep has the potential to set off tissue-specific epigenetic gene expression, and metabolic changes that are associated with an increase in fat and decrease in lean muscle mass. It causes

DNA hypermethylation in adipose tissue near the transcription start site (TSS) of the CD36 gene, the expression of which is deregulated in obese and type 2 diabetic patients. (3)

Extensive findings from numerous human studies spanning multiple tissue types have independently reported that dreadful experiences are associated with increased methylation at the exon 1F NGFI-A binding sequence. A drop in hippocampal glucocorticoid receptor (GR) expression and plummeting of stress responses in adulthood have been found to be associated with histone post-translational modifications of GR promoter in the hippocampus. (4)

Researchers have also demonstrated how stress is linked with continual disruptions in the hypothalamic-pituitary-adrenal (HPA) axis and psychiatric symptoms. It causes disturbance in HPA functioning at an epigenetic level and generates long-lasting changes in the stress regulatory system that eventually puts an individual at a risk of psychopathology.

Excess methylation of a promoter sequence within the NR3C1 gene attenuates the expression of GR, whose function is to bind to cortisol and other glucocorticoids to create a negative feedback loop within the HPA axis. (5)

The advent of eMRI or epigenetic MRI in the most recent days has promisingly substantiated the epigenetic phenomenon in the brain. A team at the University of Illinois, has managed to capture DNA methylation ( a prominent epigenetic mechanism) changes in the brain . Research in the fields related to brain growth and development, learning, and response to stress can now take advantage of technology to understand the epigenetic changes.

Hence, there is more to the bigger picture when it comes to long-term fright reactions caused by scary movies and TV shows and we need to be wary of the type of content we consume, especially at a young age lest it should seep deeper into our skins to prompt unfavorable molecular changes.

References:

1. Psychology and neurobiology of horror movies Lauri Nummenmaa, PhD, Professor Turku PET Centre, Department of Psychology and Turku University Hospital, University of Turku, Finland
2. Thau L, Gandhi J, Sharma S. Physiology, Cortisol. [Updated 2021 Sep 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538239/
3. https://www.genengnews.com/news/epigenetics-of-sleep-loss-linked-with-weight-gain-and-muscle-loss-in-humans/#:~:text=Epigenetics%20of%20Sleep%20Loss%20Linked%20with%20Weight%20Gain%20and%20Muscle%20Loss%20in%20Humans,-August%2024%2C%202018&text=Studies%20by%20researchers%20at%20Uppsala,and%20an%20increase%20in%20fat
4. Zhang, T. Y., Labonté, B., Wen, X. L., Turecki, G., & Meaney, M. J. (2013). Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 38(1), 111–123. https://doi.org/10.1038/npp.2012.149
5. Liu, P. Z., & Nusslock, R. (2018). How Stress Gets Under the Skin: Early Life Adversity and Glucocorticoid Receptor Epigenetic Regulation. Current genomics, 19(8), 653–664. https://doi.org/10.2174/1389202919666171228164350

# Let's trace

1 **1942**
The term "epigenetics" was coined by Conrad Waddington

2 **1948**
The serendipitous discovery of 5-methylcytosine by Rollin Hotchkiss

3 **1948**
Hermann Muller introduces the term dosage compensation

4 **1958**
David L. Nanney claimed the existence of two cell regulatory systems – one genetic and one epigenetic

5 **1960**
Helen Crouse first used the term 'imprint'

6 **1961**
Lyon proposed that the genetically inactivated X-chromosome 'can be either paternal or maternal in origin'

7 **1964**
Allfrey, Faulkner, Mirsky proposed that modification of histones can regulate gene expression

8 **1971**
Chromosomal imprinting in mammals first recognised by Cooper et al.

9 **1975**
Holliday, Pugh and Riggs propose that DNA methylation controls gene expression, is heritable following cell division

10 **1978**
Metastable epialleles first described in mice

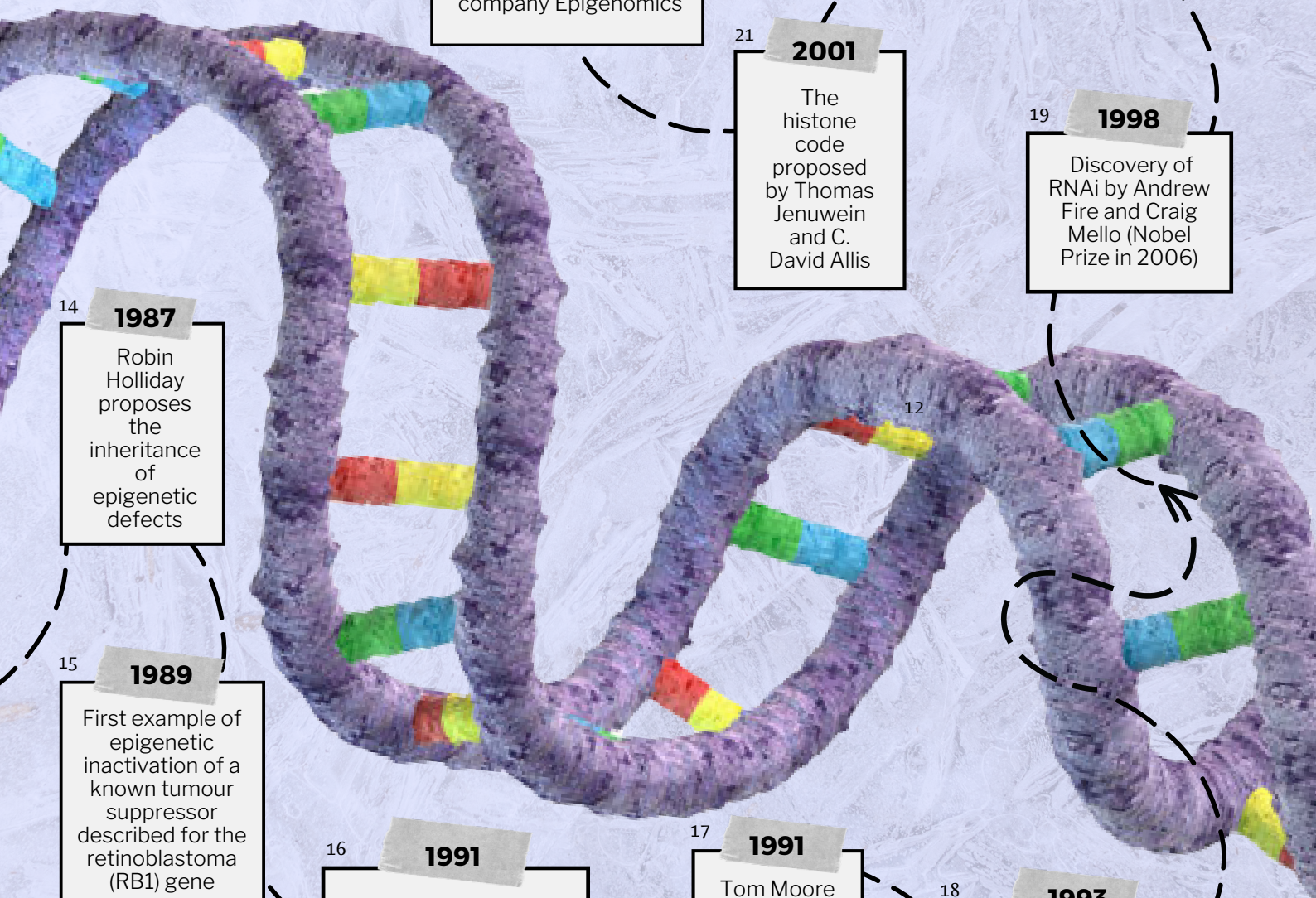
11 **1980s**
Bestor (MIT) identified the first mammalian DNA methyltransferase from mouse cells (DNMT1)

12 **1983**
Feinberg, Vogelstein and Ehrlich demonstrate that DNA hypomethylation is a ubiquitous feature of human cancers

13 **1985**
CpG islands first recognised

Picture Credit: A KYU Design

# the epigenetic timeline!



23 **2010**

International Human Epigenome Consortium (IHEC)

24 **2010 - Present**

Nutritional epigenetics and use fo methylation patterns for diagnostics has started gaining momentum

22 **2003**

Human Epigenome Project (HEP) formed by the Wellcome Trust Sanger Institute and the biotechnology company Epigenomics

20 **2000**

CTCF identified as a key mediator of imprinting at the H19/Igf2 locus

21 **2001**

The histone code proposed by Thomas Jenuwein and C. David Allis

19 **1998**

Discovery of RNAi by Andrew Fire and Craig Mello (Nobel Prize in 2006)

14 **1987**

Robin Holliday proposes the inheritance of epigenetic defects

15 **1989**

First example of epigenetic inactivation of a known tumour suppressor described for the retinoblastoma (RB1) gene

16 **1991**

X-inactivation was shown to be dependent on a region on the X-chromosome, designated the X-inactivation centre (XIC)

17 **1991**

Tom Moore and David Haig proposed the 'parental conflict' theory

18 **1993**

Bryan Turner proposed that post-translational modifications of the amino-terminal tails of histones encodes epigenetic information

# EPIGENETIC CONSTRUCTION OF MEMORY



SAUMYA ARORA and RYTHEM GOYAL
B.Sc. (Hons.) Biochemistry, III year

One of the wondrous characteristics of all organisms is the memory of their actions, though retained at different rates in different organisms. Have you ever decoded the fact that even an Alzheimer's patient doesn't forget how to walk or talk? The necessity for cementing the bricks of our actions to build a memory that we frequently access to carry out a task. It could be as simple as typing for instance, which requires a memory of finger movements, the sequence of alphabets over the keyboard and the spellings of several words that we intend to insert to formulate a meaningful sentence.

The mechanism behind storing all the information is the modulation of existing information in the DNA of our cells. These modulations are meiotically and mitotically heritable changes in gene expression but not encoded in the DNA sequence of the genome - affected by environment, dietary intake, social interactions etc. What are these changes? Well, these are mostly acetylation and methylation of the histones and the cytosines in DNA sequences respectively. The methylation in DNA is mostly observed at CpG islands- or the sites with cytosine separated from an adjacent guanine by a phosphate, generally at the promoter of genes that tend to downregulate the activity of the promoter and thus lowering protein production. These changes allow differentiated cells to express only specific proteins while genes for others proteins remain 'silent'; for instance, no brain cell would produce liver enzymes and no pancreas cells express brain-specific proteins. [5] histone acetylation (catalysed by histone acetyltransferase- HAT) is often associated with the enhanced rates of transcription, while histone deacetylation (catalysed by Histone DeAcetylases-HDAC) is associated with repressed transcription of the gene. [6]

But one may wonder, how do we even detect the epigenetic changes, more so, how can one determine its influence on neuronal cells? In a bid to explain this, we refer here to a study carried out by scientists from the European Molecular Biology Organisation (EMBO), Spain where they had genetically modified nematode worms to carry the genes for fluorescent proteins that showed minimal activity at a temperature of about 20℃ but exhibited high fluorescence at about 25℃. The worms, when moved after 5 generations from a warm environment to a cooler temperature, retained high fluorescence exhibiting 'environmental memory' of the warmer climate for 14 generations that was inherited without any in-between experience of warm climate. [3]

The question “How is epigenetics really influencing any of this?” still persists. So let’s unfold the main plot here. Memory formation or recall is often associated with histone modification which can be induced by nucleosome variation which in turn is introduced by variation of histone protein/subunit isoforms included in the nucleosome. This varies the interaction between DNA and nucleosome histones in a homotypic or heterotypic orientation, cementing the memory formation via transcriptional accessibility to linker/core DNA in nucleosomes (fig.-1) [1].

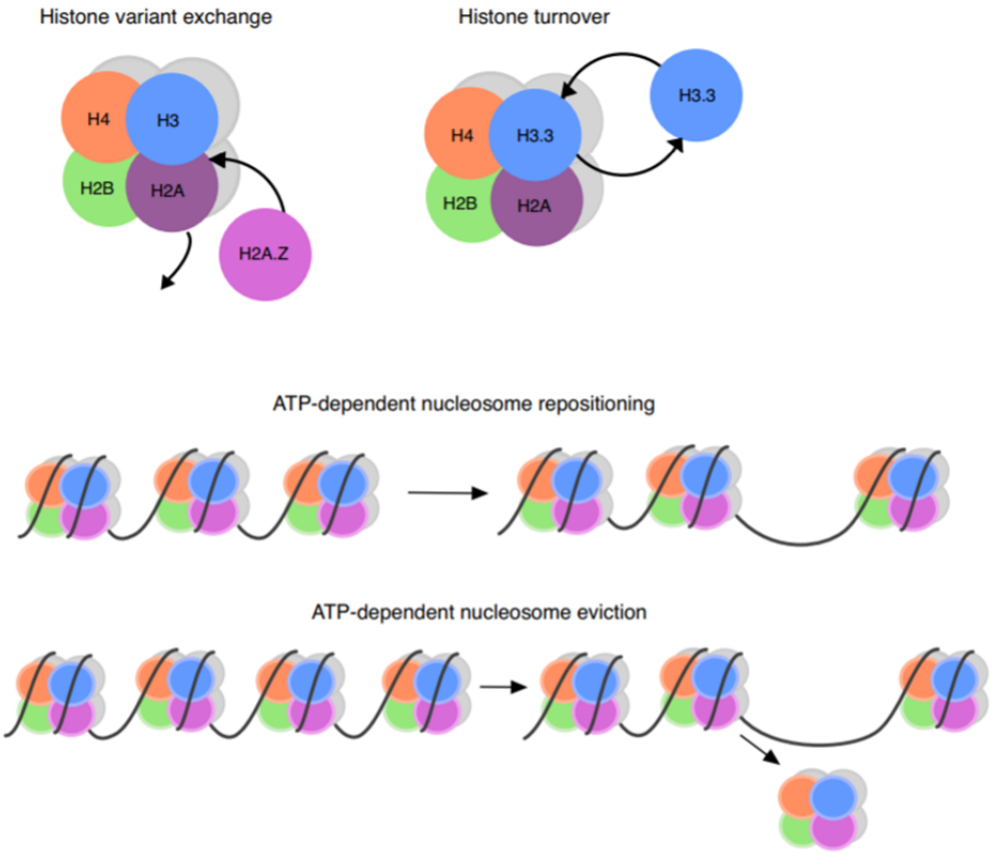



Fig.1- Regulation of chromatin dynamics via Histone variation. (Iva B Zovkic, 2021)

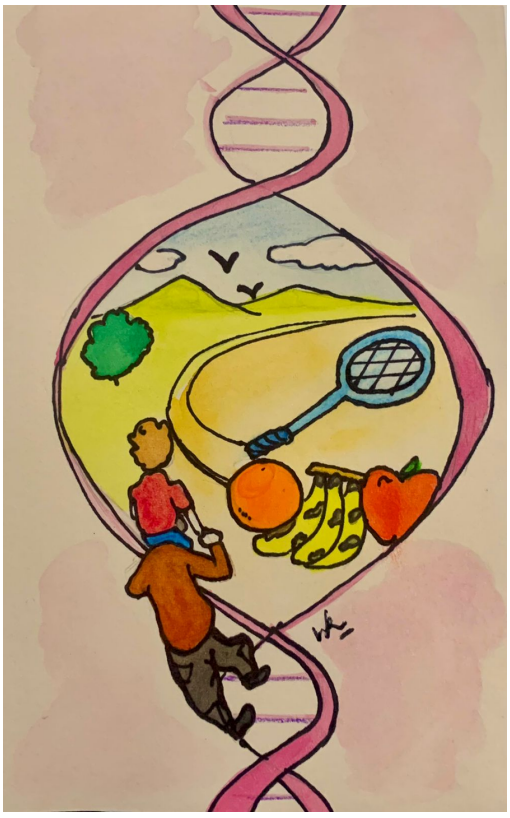
Now its time to understand its implications in the real world. Let’s see the instance of Alzheimer’s Disease (AD). Increased memory loss and confusion, inability to learn new things, difficulty with language and problems with reading, writing, and working with numbers, difficulty organising thoughts and thinking logically, shortened attention span and problems coping with new situations are a few characteristic symptoms of an AD patient. The memory impairment suffered by patients of AD, is subject to epigenetic regulation which can serve as a way to its treatment. Studies have found various genes which undergo DNA methylation and this phenomenon is being used as a biomarker of Alzheimer’s disease. The methylation and demethylation of promoter regions of certain genes alter the deposition of amyloid-beta protein in aged brains, again signifying Alzheimer’s. It has also been found that amyloid-beta treatment changes the DNA methylation profile in differentiated human neurons and that it could change the methylation status of some cell-fate genes. Moreover, few Histone DeAcetylases have been found in decreased levels in mouse models of AD, leading to enhanced cognitive impairment. Additionally, one of the HDACs is found to be co-localized with Tau protein in AD Hippocampus, which has been associated with tau aggregation (hallmark of AD) and another HDAC responsible for lowering tau concentrations were observed to have lower levels in AD

cortex. Some of these HDACs, linked to aggravation of AD symptoms have been observed in memory associated regions of the brain as well. Furthermore, a microarray analysis exhibited dysregulated expression patterns of non-coding RNAs in AD mouse hippocampus, playing a role in cognitive impairment.

Epigenetics is much more than just DNA methylation or chromosome remodelling via histone modifications, it is inclusive of all the environmental, biogeographic, interactions and even nutritional intake. The biochemical findings have not reached their conclusion, but the epigenetic mechanisms influencing memory have been well established by several pieces of evidence. These mechanisms can, thus, be regulated to minimise neuropsychological impairment in AD patients.

References:

1. Iva B Zovkic,Epigenetics and memory: an expanded role for chromatin dynamics, Current Opinion in Neurobiology, Volume 67, 2021, Pages 58-65, ISSN 0959-4388, https://doi.org/10.1016/j.conb.2020.08.007.
2. Yan Zheng, Aiyi Liu, Zi-Jun Wang, Qing Cao, Wei Wang, Lin Lin, Kaijie Ma, Freddy Zhang, Jing Wei, Emmanuel Matas, Jia Cheng, Guo-Jun Chen, Xiaomin Wang, Zhen Yan, Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease, Brain, Volume 142, Issue 3, March 2019, Pages 787–807, https://doi.org/10.1093/brain/awy354
3. Scientists Have Observed Epigenetic Memories Being Passed Down For 14 Generations
4. Ji-Song Guan, Hong Xie, XinLu Ding, The role of epigenetic regulation in learning and memory, Experimental Neurology, Volume 268, 2015, Pages 30-36, ISSN 0014-4886, https://doi.org/10.1016/j.expneurol.2014.05.006.
5. Molfese D. L. (2011). Advancing neuroscience through epigenetics: molecular mechanisms of learning and memory. Developmental neuropsychology, 36(7), 810–827. https://doi.org/10.1080/87565641.2011.606395
6. Liu X, Jiao B and Shen L (2018)The Epigenetics of Alzheimer'sDisease: Factors and Therapeutic Implications. Front. Genet. 9:579.doi: https://doi.org/10.3389/fgene.2018.00579



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# Epigenetics and Schizophrenia

SHIVANSH SINGH
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Introduction

Researchers have been studying epigenetic mechanisms for decades and trying to use them for treating diseases. Methylation, acetylation, and phosphorylation are among the most important epigenetic processes. While epigenetic processes are essential to many organism functions, they can also have adverse health and behavioural effects if they are not performed properly. DNA methylation changes were, first observed in cancerous tissues back in 1083. Chromatin modifications that involve acetylation, phosphorylation affect gene expression by altering the structure of chromatin. If the chromatin is tightly folded it will not be expressed, and open chromatin is fully functional. In medicine, it may find application in the delivery of drugs and the treatment of diseases by altering gene expression. We would probably expect scientists to pragmatically be working towards accessing these genes and altering their expressions independently to relieve the patients from their diseases, right?

Well...yes, but it's easier said than done. We need to keep factors like cellular composition in mind. DNA methylation patterns are highly specific and depend on the cell type. The cellular composition also varies in response to stress and ageing, which alters the epigenetic variations based on different tissue-specific profiles, thus a careful measurement of the DNA methylation profile is required. Furthermore, cells from target tissues are not typically available in sufficient numbers to generate statistically accurate results. This is why surrogate tissues (e.g., Whole blood) are used in order to reflect epigenomic changes similar to the target tissues. Therefore an ideal method of correcting this cellular bias would be to isolate and profile individual blood subsets, to generate statistically sound and viable results.

Epigenetic studies related to psychological disorders

Can psychological issues be associated with DNA methylation or protein acetylation, and whether such epigenetic modifications could help in alleviating the effects of psychological adversities? In a study conducted in 2013, Perroud et al. took 115 patients with Borderline Personality Disorder and studied the BDNF gene, which is important for regulating synaptic plasticity. After a 4-week course of DBT-intensive treatment, BDNF-DNA methylation levels had increased. Bipolar patients showed a higher number of DNA methylations. Other such studies, which included a control group and a replication sample also showed similar results wherein DNA methylation and the severity of psychiatric disorders were seen to be negatively correlated.

Another promising study was by Walton, et al. (2016), where they investigated DNA methylation in cord blood and blood samples taken at a later stage in life to see the association of substance use and

epigenome modifications. Early age of abuse onset and higher levels of substance abuse in teens were associated with DNA methylation variations at 65 CpGs at birth. Altogether, these CpG sites appeared to be involved in adolescent substance abuse induced by maternal smoking. In simple words, situational adversities during adolescence trigger DNA methylations at various CpG sites, which can affect an individual's personality and mental health later in life. These studies have brought us closer to the fact there is a significant role of epigenetic modification in psychiatry and how we perceive it.

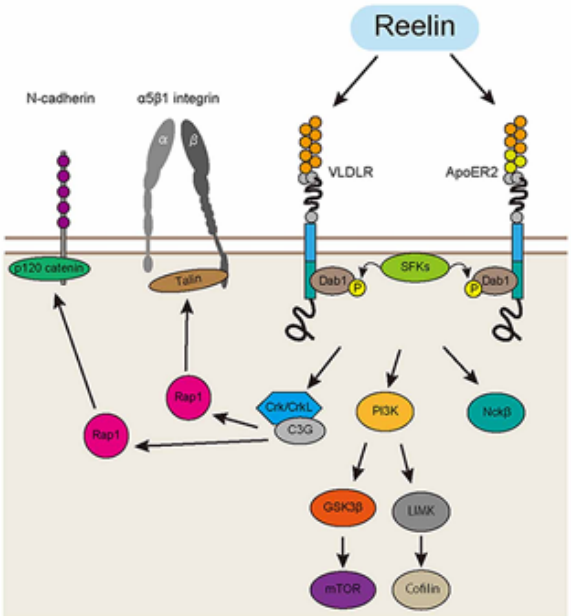
Schizophrenia

Schizophrenia ( SCZ) is one of the strangest maladies of the mind ever studied. SCZ is a serious mental disorder characterized by loss of cognitive abilities, behavioural impairments, delusional thoughts and hallucinations, only to deteriorate over time. The gravity of the severity of the disease can be assessed by the fact that the patients require lifelong treatment and therapies. No specialized drugs have yet been developed for SCZ. The medications usually prescribed are antipsychotics namely Aripiprazole, Asenapine etc, which target the release of dopamine, a neurotransmitter.

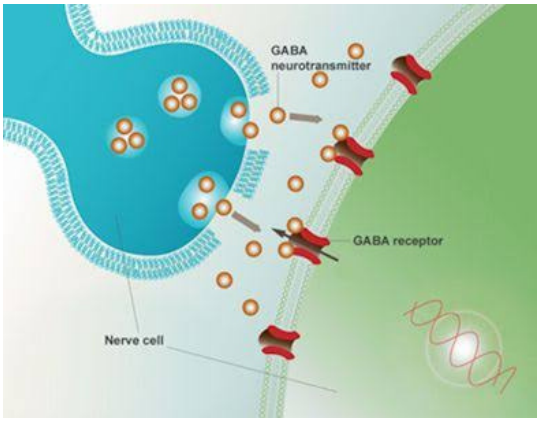
Epigenetics of Schizophrenia (SCZ)

Expression of genes such as reelin (RELN), brain-derived neurotrophic factor (BDNF), glutamic acid decarboxylase-1 (GAD) and glucocorticoid receptors are altered in SCZ patients. Studies done on schizophrenic patients by Abdolmaleky HM, et al. have revealed hypomethylation of membrane-bound catechol-O-methyltransferase (MB-COMT) promoter on analysis of post-mortem brain samples. Epigenetic dysregulation of hydroxytryptamine receptor (HTR2A) has also been seen in schizophrenia.

RELN gene is closely related to higher brain functions because it encodes an important ECM glycoprotein named 'Reelin'. By controlling cell-cell interactions, Reelin is known to help in the regulation of different processes of neuronal positioning and migration in the developing brain. Reelin was first discovered in 1951 by D.S Falconer and since then, there have been many speculative reports on its genetic variation to Schizophrenia and other complex disorders. Within the Chinese population existence of a gender-specific (women) association between SNPs in RELN, have been reported by studies of Liet et al (2013), Shifman et al. (2008) and Kuang et al. (2011) on single nucleotide polymorphism (SNPs). Reelin is often connected to higher brain function since its absence leads to the loss of cognitive functions in mice and rodents. An epigenetic drug named Valproate, which is known as a mood enhancer drug has been tested in clinical trials. Valproate-enhanced histone 3 content has




Reelin signaling pathway in the developing cortex (Europe PMC, 2016)



(Gamma-aminobutyric acid (GABA) Molecule of the Month - July 2015 (HTML version), 2015)

been shown to prevent RELN gene promoter hypermethylation in mice, which encodes reelin protein, correcting the epigenetics-induced brain abnormalities in the mice.

Expression of the GAD-1 gene is shown to be decreased in schizophrenia patients. GAD-1 is responsible for the encoding of GABA(gamma-aminobutyric acid) which in adult mammalian brains is a neurotransmitter known for reducing the excitation potential of neurons. GABA regulates chloride ion flow across the neuronal cells (GABA -ergic cells) through ligand-activated ion channels, thereby exhibiting depolarization or hyperpolarization across the membrane depending upon Cl ion flow inside or outside the cell. Thus, GABA is an important neurotransmitter. GABA is relevant to us because GAD67 and GAD65 are expressed in the part of the brain where GABA acts.

Patients suffering from SCZ showed substantial GAD mRNA expression dysregulation in their dorsolateral prefrontal cortex(DLPFC) of the brain, which is important for our working memory. Lower GAD levels in DLPFC, therefore account for the loss of memory that is a general symptom of such patients. A whooping eightfold decrease in DNA methylations was observed at the GAD1 promoter in the prefrontal cortex of the patients in a study conducted by Huang et al, confirming the importance of epigenetic changes in schizophrenia.

## Conclusion

All in all, we can conclusively say that epigenetics plays a vital role in idiopathic psychiatric disease pathogenesis, including schizophrenia. Studying the epigenetic modifications caused in these diseases, and developing the molecular basis for regulating such diseases through drugs and different therapeutic procedures, could potentially help treat mental illnesses.

References:

1. Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M. E., Furrer, S., Ardu, S., Krejci, I., Karege, F., & Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. Translational psychiatry, 3(1), e207. https://doi.org/10.1038/tp.2012.140
2. Kumsta R. (2019). The role of epigenetics for understanding mental health difficulties and its implications for psychotherapy research. Psychology and psychotherapy, 92(2), 190–207. https://doi.org/10.1111/papt.12227
3. Lowe, R., & Rakyan, V. K. (2014). Correcting for cell-type composition bias in epigenome-wide association studies. Genome medicine, 6(3), 23. https://doi.org/10.1186/gm540
4. Abdolmaleky, H. M., Cheng, K. H., Faraone, S. V., Wilcox, M., Glatt, S. J., Gao, F., Smith, C. L., Shafa, R., Aeali, B., Carnevale, J., Pan, H., Papageorgis, P., Ponte, J. F., Sivaraman, V., Tsuang, M. T., & Thiagalingam, S. (2006). Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Human molecular genetics, 15(21), 3132–3145. https://doi.org/10.1093/hmg/ddl253
5. Abdolmaleky, H. M., Yaqubi, S., Papageorgis, P., Lambert, A. W., Ozturk, S., Sivaraman, V., & Thiagalingam, S. (2011). Epigenetic dysregulation of HTR2A in the brain of patients with schizophrenia and bipolar disorder. Schizophrenia Research, 129(2-3), 183–190. https://doi.org/10.1016/j.schres.2011.04.007
6. Ishii, K., Kubo, K., & Nakajima, K. (0001, January 01). Reelin and neuropsychiatric disorders. Retrieved March 6, 2022, from https://www.frontiersin.org/articles/10.3389/fncel.2016.00229/full
7. Huang H-S, Akbarian S (2007) GAD1 mRNA Expression and DNA Methylation in Prefrontal Cortex of Subjects with Schizophrenia. PLoS ONE 2(8): e809. https://doi.org/10.1371/journal.pone.0000809

# THE EPIGENETICS OF ADDICTION

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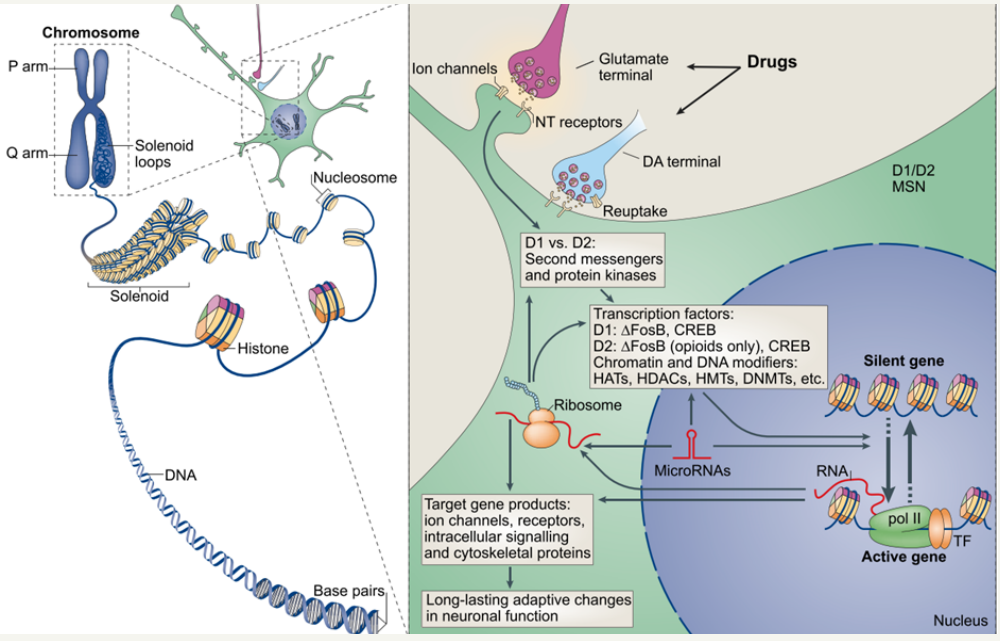
Drug dependence, a menace to society, can be defined as a chronic and progressive addiction to a specific psychoactive substance. It is a result of persistently intense consumption of any substance. The vulnerability to addiction can emerge through both genetic predisposition and environmental risks. The ill-effects of drug addiction are not new; and include social, behavioural, psychological and physiological dysfunction.

One part of an important lingering question that has remained unanswered for decades- the molecular mechanisms behind addiction, can now be answered in the light of our current knowledge of epigenetics. Upon drug exposure, the nerve cells inside the brain's reward circuitry are altered at the epigenetic level. On constant consumption, the circuits adapt to a stimulus generated on exposure to the drug which is far stronger and more persistent than natural rewards, causing an insufficiency in its absence. This leads to a chronic dependency and what we call addiction. Due to the long-term modifications in brain function, drug-related behavioural aberrations are salient characteristics of addiction.

Addiction drugs act at the synaptic targets via neurotransmitters, in this case, the glutaminergic neurons of the hippocampus, prefrontal cortex and amygdala. These produce excitatory inputs which are received by dopaminergic receptors which innervate into the medium spiny neurons (MSNs) of the nucleus accumbens (NAc). The NAc is a part of the mesolimbic dopamine circuitry which essentially serves to maintain the evolutionary zeal of perpetuation of one's species, by regulating activities like food intake and sex. Certain drugs stimulate dopamine



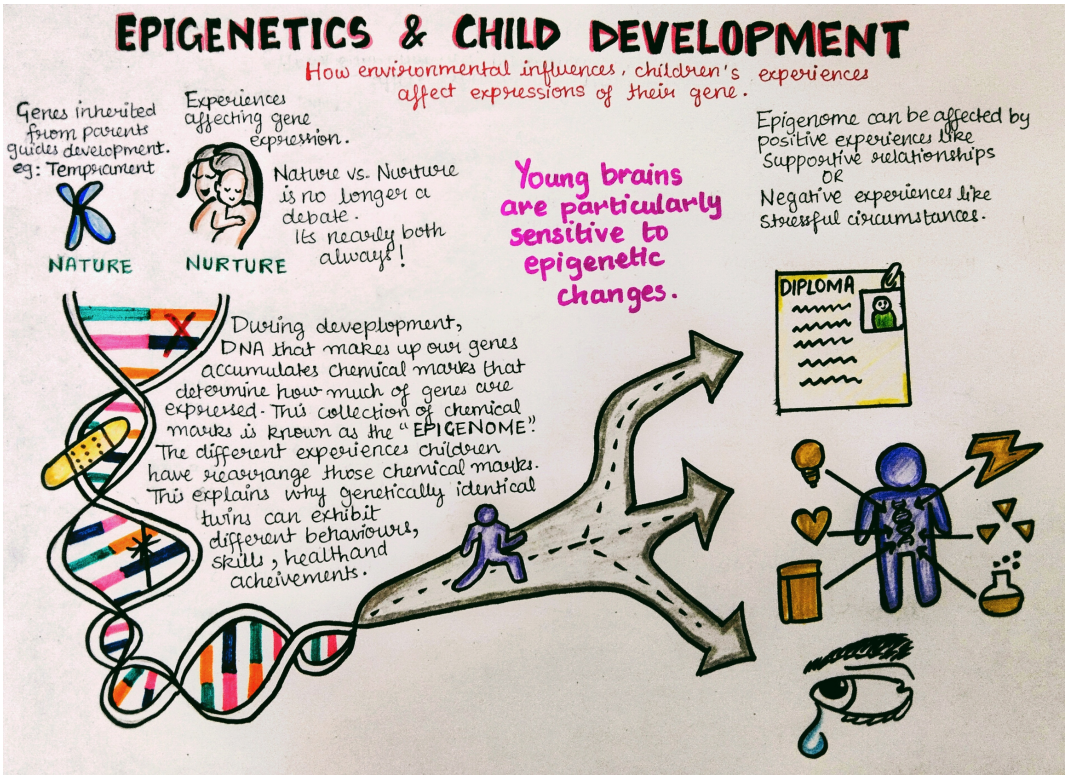

Integrated Scheme of Epigenetic and Synaptic Mechanisms of Addiction (Nestler & Lüscher, 2019) [3]

secretion as well while inhibiting GABAergic neurons. Thus, both the dopaminergic (indirect effect) and glutaminergic neurons (direct effect) release neurotransmitters that signal the D1 and D2 dopamine receptors, via GPCRs. These in turn affect the downstream signalling, leading to the activation of certain protein kinases which causes the phosphorylation of CREB (cAMP response element-binding protein). The CREB-like proteins act as a chromatin modifier and cause increased acetylation of certain genes by regulating the activity of enzymes like Histone acetylase (HAT) and HDAC (Histone deacetylase). Hereon, the type and extent of exposure are associated with the activity of HAT and HDAC on certain specific gene promoters. Long-lasting drug intake brings about not only transcriptional changes correlated with gene expression but structural plasticity as well as electrophysiological changes. Epigenetic modifications mediate gene priming and desensitization as well. This reduces the expression of these genes thus looping back into promoting the rewarding property, hence contributing to the addiction pathogenesis.

The science exponentiation of the cause is of no use if its application is not translatory. Thus, many teams globally monitor the level of epigenetic changes that occur during withdrawal stages and adjust these markers to treat people struggling to relieve themselves from addiction. One of the studies, carried out by the Medical University of South Carolina suggests that enhanced input of HDAC during withdrawal, though may not contribute to blocking genes that promote drug-seeking behaviour, are impactful in preventing relapse. Thus, epigenetics-based therapeutics hold promise to treat addiction by a more effective and pain-free approach.

References:

1. Hamilton, P. J., & Nestler, E. J. (2019). Epigenetics and addiction. Current Opinion in Neurobiology, 59, 128–136. https://doi.org/10.1016/j.conb.2019.05.005
2. Robison, A. J., & Nestler, E. J. (2011). Transcriptional and epigenetic mechanisms of addiction. Nature Reviews Neuroscience, 12(11), 623–637. https://doi.org/10.1038/nrn3111
3. Nestler, E. J., & Lüscher, C. (2019). The Molecular Basis of Drug Addiction: Linking Epigenetic to Synaptic and Circuit Mechanisms. Neuron, 102(1), 48–59. https://doi.org/10.1016/j.neuron.2019.01.016




Vani
B.Sc. (Hons.), II Year

# CANCER AND EPIGENETICS

NIMISHA KHURANA
B.Sc. (Hons.) Biochemistry, III year

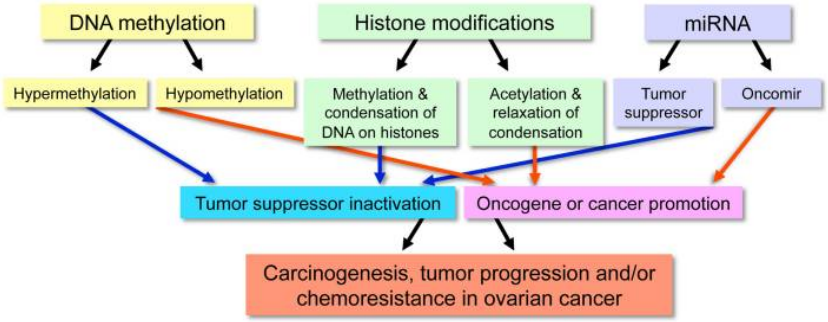
Cancer is a condition wherein some of the body's cells tend to grow uncontrollably and move towards other parts of the body [1]. This invasive condition can initiate from abnormal proliferation of any type of cells in the body, therefore there are numerous categories of cancers, which may vary substantially in their activity and response to therapy [1].

It was traditionally thought that the major cause for neoplasia was the accumulation of genetic mutations [2]. But recently it was discovered that cancer can be a manifestation of both genetic and epigenetic modifications which cause alterations in the expression of oncogenes and tumour suppressor genes. Gene products of Oncogenes are the proteins that play a role in driving the cell cycle forward, permitting the cell to advance from one of the gap phases (G1 or G2 phase) which are the prime checkpoints of the cell cycle to either DNA replication (Synthesis phase- S phase) or cell division (Mitosis phase- M phase) [1]. Under normal conditions, genes that encode proteins controlling the progress of critical cell cycle processes are called proto-oncogenes. But, their altered form is called oncogenes – which leads to the generation of abnormal protein products that exhibit augmented activity (gain of function) and therefore result in unregulated cell cycle advancement. Conversely, protein products of Tumour suppressor genes inhibit cell cycle progression and stimulate programmed cell death; silencing of these genes (loss of function) which act as a brake control under normal conditions affects the cell just as much as overexpression of oncogenes. Thus either or both these states lead to loss of checkpoint control [1]. This dysregulation allows the cell to pass through consequent phases of the cell cycle resulting in uncontrolled cell division thereby promoting tumour progression.

Interestingly, the aetiology of cancer involves hereditary as well as environmental effects, studies have shown that only 5-10% of cancers are caused by inherited genetic mutations; the remaining 90-95% of cancers are enkindled by variable agents such as environmental factors, hormone levels and other physical factors [3]. Therefore, epigenome dysregulation is a prevalent cause of cancer [4].

A common definition of epigenetics concerns DNA-template regulation that occurs within the chromatin. A variety of epigenetic mechanisms are capable of changing the accessibility of chromatin to transcription machinery or regulators on a global as well as local level through DNA modifications or nucleosomal rearrangement. Hence, they lead to a change of gene expression by altering their

accessibility to transcriptional machinery and without altering the primary DNA sequences. These mechanisms are necessary for a cell to maintain normal development and gene expression in different organs and hence unusual epigenetic regulation can affect gene expression leading to tumorigenesis. Epigenetic changes such as DNA methylation and histone modifications have been extensively linked with tumours [2].




Effect of epigenetic changes on cell cycle regulation genes in ovarian cancer cells.
(Nguyen et al., 2014)

DNA methylation is a process in which the 5th carbon of the cytosine residues preceding a guanine (5'–C– phosphate–G–3') undergoes covalent modification [5]. This change alters the domain of DNA that regulates DNA expression by transcription modulation. Change in DNA methylation patterns is the most widely seen alteration in cancer cells and it is more prevalent than even genetic modifications [6]. Research on cancer cells in mammals shows that the epigenome is characterised by a genome-wide decrease of DNA methylation called hypomethylation and hypermethylation i.e increase in methylation of specific regions called CpG islands present in the promoter region [2]. DNA analysis confirms that about 5-10% of CpG in the promoters are unusually methylated in cancer cells, this hypermethylation is often associated with transcriptional silencing of tumour suppressor genes; which control cell cycle and DNA repair including RB, BRCA1/2, and PTEN. The mechanism underlying this inactivation of a gene is closely associated with closed chromatin structure and compact DNA packaging which prevents their expression by making it inaccessible to transcriptional machinery. [2, 7]

Mass spectrophotometric data has also detected unusual histone protein modification in cancer cells. Varying patterns of methylation on histone proteins such as the addition of mono-, di- or tri-methyl group(s) at their Lys or Arg residue along with other covalent modifications such as acetylation, ubiquitination, phosphorylation and sumoylation have been observed in malignant cells [6]. The type and the site of these covalent modifications regulate the function of the proteins

**Table 1. Epigenetic Aberrations among Different Tumor Types.***

| Type of Cancer | Epigenetic Disruption |
|---|---|
| Colon cancer | CpG-island hypermethylation (*hMLH1*, *p16$^{INK4a}$*, *p14$^{ARF}$*, *RARB2*, *SFRP1*, and *WRN*), hypermethylation of miRNAs (*miR-124a*), global genomic hypomethylation, loss of imprinting of *IGF2*, mutations of histone modifiers (*EP300* and *HDAC2*), diminished monoacetylated and trimethylated forms of histone H4 |
| Breast cancer | CpG-island hypermethylation (*BRCA1*, E-cadherin, *TMS1*, and estrogen receptor), global genomic hypomethylation |
| Lung cancer | CpG-island hypermethylation (*p16$^{INK4a}$*, *DAPK*, and *RASSF1A*), global genomic hypomethylation, genomic deletions of *CBP* and the chromatin-remodeling factor *BRG1* |
| Glioma | CpG-island hypermethylation (DNA-repair enzyme *MGMT*, *EMP3*, and *THBS1*) |
| Leukemia | CpG-island hypermethylation (*p15$^{INK4b}$*, *EXT1*, and *ID4*), translocations of histone modifiers (*CBP*, *MOZ*, *MORF*, *MLL1*, *MLL3*, and *NSD1*) |
| Lymphoma | CpG-island hypermethylation (*p16$^{INK4a}$*, *p73*, and DNA-repair enzyme *MGMT*), diminished monoacetylated and trimethylated forms of histone H4 |
| Bladder cancer | CpG-island hypermethylation (*p16$^{INK4a}$* and *TPEF/HPP1*), hypermethylation of miRNAs (*miR-127*), global genomic hypomethylation |
| Kidney cancer | CpG-island hypermethylation (*VHL*), loss of imprinting of *IGF2*, global genomic hypomethylation |
| Prostate cancer | CpG-island hypermethylation (*GSTP1*), gene amplification of polycomb histone methyltransferase *EZH2*, aberrant modification pattern of histones H3 and H4 |
| Esophageal cancer | CpG-island hypermethylation (*p16$^{INK4b}$* and *p14$^{ARF}$*), gene amplification of histone demethylase *JMJD2C/GASC1* |
| Stomach cancer | CpG-island hypermethylation (*hMLH1* and *p14$^{ARF}$*) |
| Liver cancer | CpG-island hypermethylation (*SOCS1* and *GSTP1*), global genomic hypomethylation |
| Ovarian cancer | CpG-island hypermethylation (*BRCA1*) |

Examples of epigenetic changes as biomarkers of different kinds of cancer.
(Esteller, 2008)

by either activating or repressing their expression therefore this modification has been correlated with cancer. A few notable examples of this effect can be concluded by the gene repression caused by the removal of the acetyl group present on Lys16 residue (H4K16ac) and loss of trimethylation on Lys20 residue (H4K20me3) of the H4 subunit of Histone proteins [5]. Additionally, A remarkable observation suggests that HDACs (Histone deacetylases); a category of enzymes that function to remove the acetyl groups present on proteins are found to be upregulated in cancer cells; demonstrating their importance as targets for epigenetic therapy of cancer [7].

Therefore, epigenetic changes are tightly correlated with cancer development and progression as they may cause repression or activation of proto-oncogenes and tumour suppressor genes. Although these modifications can arise during the life of an individual depending on the external factors, studies also prove that these changes can be heritable if modification occurs on the DNA present in the gametes. These observations have opened a door for the application of epigenetics in therapeutics and early diagnostics of cancer. Moreover, our comprehension of the significance of epigenetics in cancer thus far can be applied to individual-specific as well as population-generic drug development based on the type of cancer. Advantages of employing epigenetics as the basis of cancer therapy include the opportunity of treatment reversibility in case of side effects [5]. This reversibility of epigenetic modifications can be attributed to the discovery of epigenetic enzymes that maintain the expression profile of a cell by adding ("writers") or removing ("erasers") the epigenetic modifications. Hence these enzymes are capable of reversing covalent modifications, for example, the Oxidise enzyme that can convert a methylated cytosine to hydroxymethyl cytosine [8]. Furthermore, If this methodology becomes efficient, it holds the potential to replace invasive and painful treatments like chemotherapy and radiotherapy.

References:


1. Cell Cycle Control, Oncogenes, Tumor Suppressors | Learn Science at Scitable. (n.d.). Retrieved March 6, 2022, from https://www.nature.com/scitable/topicpage/cell-cycle-control-by-oncogenes-and-tumor-14191459/
2. You, J. S., & Jones, P. A. (2012). Cancer Genetics and Epigenetics: Two Sides of the Same Coin? Cancer Cell, 22(1), 9–20. https://doi.org/10.1016/j.ccr.2012.06.008
3. Fymat, A. L. (2017). Genetics, Epigenetics and Cancer. Cancer therapy & Oncology International Journal, 4(2). https://doi.org/10.19080/CTOIJ.2017.04.555634
4. Chen, Q. W., Zhu, X. Y., Li, Y. Y., & Meng, Z. Q. (2014). Epigenetic regulation and cancer (Review). Oncology Reports, 31(2), 523–532. https://doi.org/10.3892/or.2013.2913
5. Sharma, S., Kelly, T. K., & Jones, P. A. (2010). Epigenetics in cancer. Carcinogenesis, 31(1), 27–36. https://doi.org/10.1093/carcin/bgp220
6. Esteller, M. (2008). Epigenetics in Cancer. New England Journal of Medicine, 358(11), 1148–1159. https://doi.org/10.1056/NEJMra072067
7. Cheng, Y., He, C., Wang, M., Ma, X., Mo, F., Yang, S., ... Wei, X. (2019). Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduction and Targeted Therapy, 4(1), 1–39. https://doi.org/10.1038/s41392-019-0095-0
8. Falahi, F., van Kruchten, M., Martinet, N., Hospers, G., & Rots, M. G. (2014). Current and upcoming approaches to exploit the reversibility of epigenetic mutations in breast cancer. Breast Cancer Research, 16(4), 412. https://doi.org/10.1186/s13058-014-0412-z

# OUTLOOKS ON EPIGENETICS

TAPASYA KHANNA
B.Sc. (Hons.) Biochemistry, II year

"Epigenetics is an antidote to the belief that our genes hardwire us"

Have you ever considered why a change in environment is beneficial in the treatment of diseases? Is it true that music, exercise, and meditation can help people overcome diseases? The researchers are attempting to answer these and other questions by looking beyond the genes that contribute to the world's heterogeneous population.

The father of genetics, James Watson (of Watson and Crick), once stated that people inherit something more than just DNA sequences. So we can go beyond genes to try and understand certain heritable traits and that takes us to the field of epigenetics. Epigenetics, according to Conrad Waddington, is the study of epigenesis, or how genotypes give rise to phenotypes for development.

Waddington, a developmental biologist tried to investigate how gene activity during development causes the emergence of a phenotype. What mechanisms are at work to bring such changes? Let us try to understand this by considering the examples of some studies performed in this field.

A simple but conflicting idea at the heart of this field is that genes have a "memory." Have you ever considered that the lives of your grandparents—the air they breathed, the food they ate, and even the things they saw—can have a direct impact on you decades later, despite the fact that you never experienced these things yourself?

Well, if you are thinking now, let me tell you that the answer to the question is- Yes.
Several studies have found evidence linking environmental factors to long-term epigenetic effects on phenotype. Epigeneticists frequently use twin studies to demonstrate how the system works. Twins exemplify genetics' amazing ability to determine human form and function regardless of environment. One of the most important methods for determining the genetic basis of a particular trait in monozygotic and dizygotic twins is 'concordance.' The actuality that monozygotic twins do not always have the same disease susceptibility has piqued epigeneticists' interest, increasing the prospect that age-related epigenetic variations are at work. As a result, young twins have similar levels of DNA methylation, whereas older twins have substantial differences in the amounts and patterns of this modification. Can non-genetic, age-dependent differences in gene markings be the cause of some twins' divergent disease predispositions? This is currently unknown.

Numerous research studies suggest that the chemistry of a mother's DNA can impact the chemistry of her offspring's DNA. A study that found maternal nurturing alters DNA methylation at the gene encoding the glucocorticoid receptor in rats suggested a possible mechanism for this effect. The experiments are done, showing that in the absence of proper nurturing, there is less methylation of the glucocorticoid receptor in the hippocampus. The hypomethylation actually results in increased expression of the receptor later in life. The implication is that the stress response pathway mediated by glucocorticoids is epigenetically corrected at the level of gene transcription. The epigenetic changes produced as a result of methylation can be inherited, thus showing trans generational effects. The figure shows that alterations that last less than one cell cycle (green asterisk, a) do not qualify as epigenetic under the definition that strictly requires heritability, whereas non-mutational changes that are transmitted from one cell to its daughters (red asterisk, b) or between generations of an organism (blue asterisk, c) do qualify.

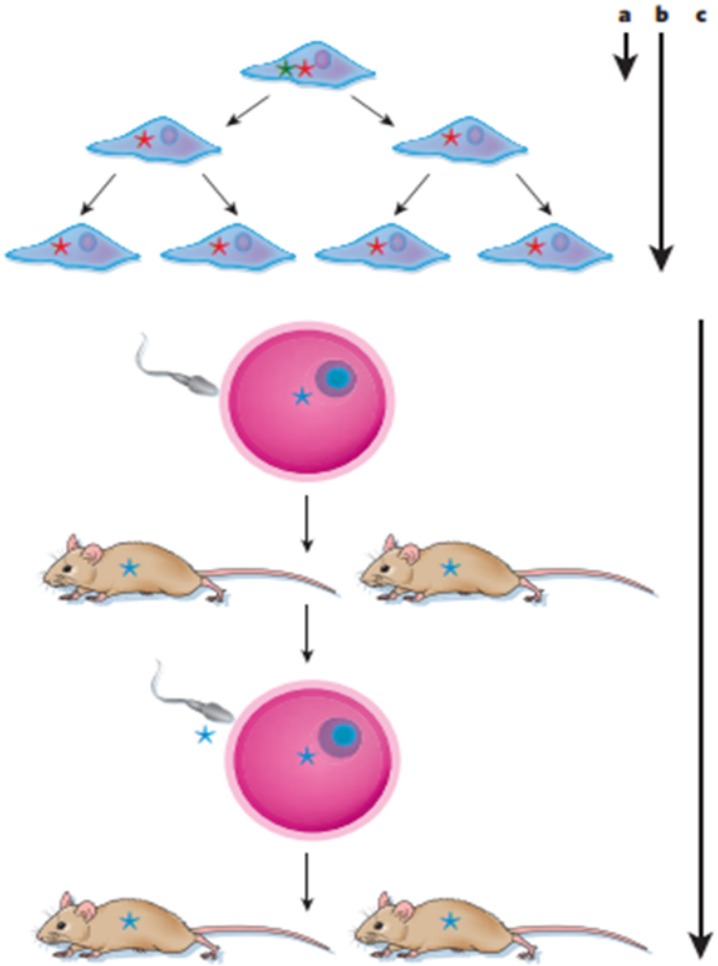



Image Courtesy: Nature

The past decade has seen great advancements in the field of epigenetics and today we are in a position to understand how the environment can affect the expression of genes over the course of a lifetime and the heritability of such changes

References:

1. (Bird, 2007) Bird, A. Perceptions of epigenetics. Nature 447, 396–398 (2007). https://doi.org/10.1038/nature05913

A woman who smokes while pregnant induces epigenetics changes in three generations at once: in herself, her unborn daughter and her daughter's reproductive cells.

# FUN SECTION




## SEROTONIN SURGE

Picture Credit: Behavioral Epigenetics: Perspectives Based on Experience-Dependent Epigenetic Inheritance (Pang et al., 2019)

# Word Search!

-Shreya Taluja,
B.Sc.(H) Biochemistry

**Find the following words in the puzzle.**
**Words are hidden ↑, ↓ , →, ← and ↘**

| | |
|---|---|
| Acetylation | Histone |
| Citrullination | Methyltransferase |
| CPG Island | Nucleosome |
| Euchromatin | Ribosylation |
| Heterosis | Ubiquitin |

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



(Answers on Pg 48)

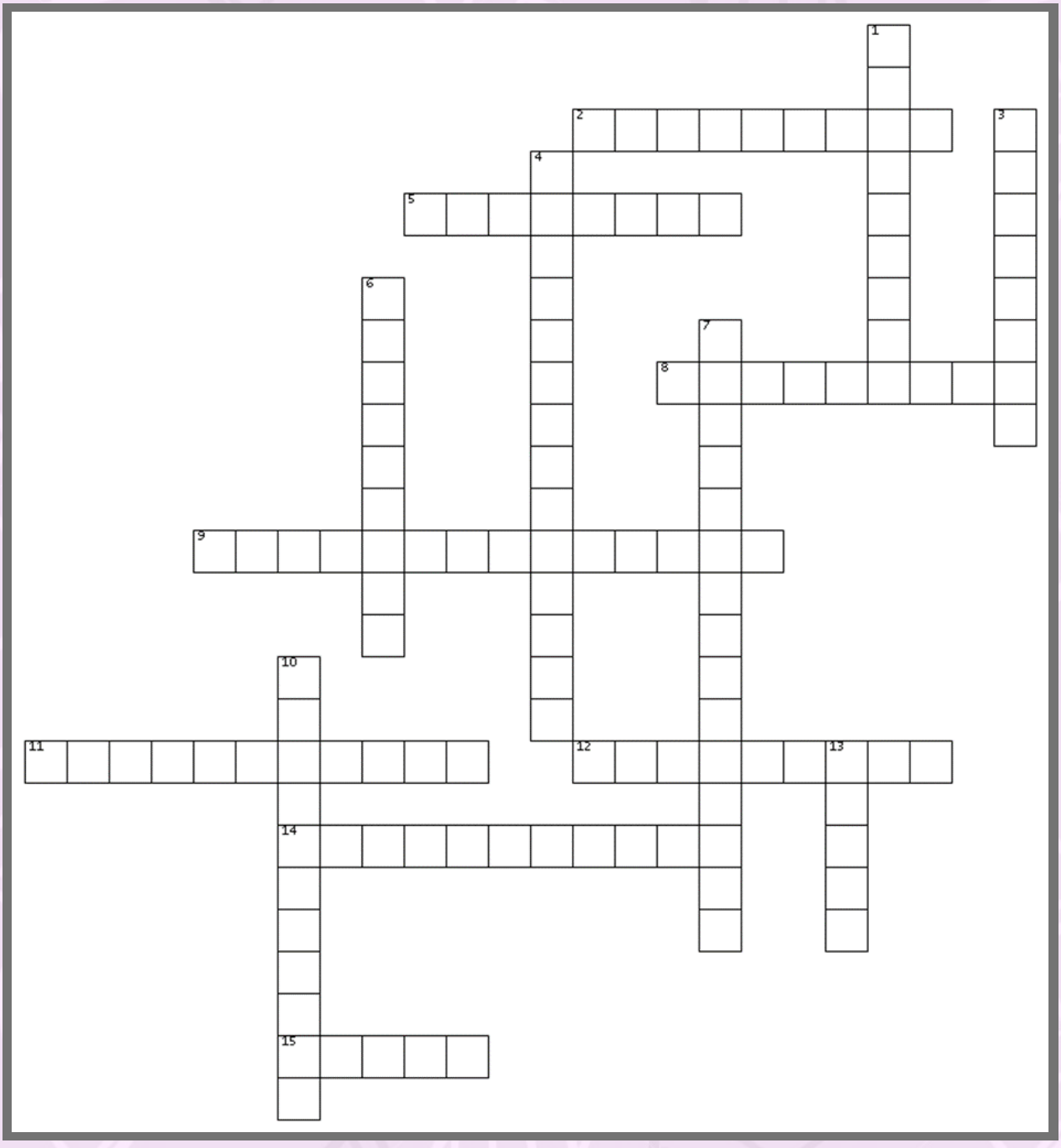
# QUIZ TIME

1. A chemical modification of DNA that does not affect the nucleotide sequence of a gene but makes that gene less likely to be expressed.
2. Igf2 is only expressed on the allele inherited from the _____
3. Which nucleotide base in human DNA is methylated at the 5' position?
4. What was the first approved epigenetic drug?
5. How many Barr bodies will a male with XXXYY chromosomes have in each of his cells?
6. The erasure and re-establishment (according to the sex of the parent) of genomic imprint occurs during the process of _____
7. The term “epigenetics’ was first introduced and defined by _____
8. In the discovery of X-chromosome inactivation, which animal was crucial?
9. The expression of X-linked genes in male and female animals is equalised by a process known as _____?
10. During replication, the enzyme responsible for maintenance of the methylation pattern in the daughter strand of DNA is _____
11. Deletion of the same region in either the maternal or paternal allele of chromosome 15 results in two clinically different diseases, _____ and _____ respectively
12. What are the three mechanisms of epigenetic regulation?
13. The process where histone modifications are identified by breaking chromatin into fragments and using an antibody that recognises a specific histone alteration.
14. What are the risks associated with skewed X chromosome inactivation?
15. Silver-Russell syndrome involves chromosomes ____ and ____.

(Answers on Pg 48)

# CROSSWORD

-Lavanya Saini, Ayesha Mirza
B.Sc.(H) Biochemistry






(Answers on Pg 48)

**DOWN**

1. A phenomenon in which gene interaction is such that one gene masks (hides) the effect of another gene at a different locus
3. A DNA segment at the start of a gene's coding sequence regulating the initiation of gene expression
4. English philosopher – who initiated a philosophy called "social Darwinism" and coined the term "survival of the fittest"
6. Phenotype produced by environmental factors alone which is same as the phenotype produced by a genotype
7. A kind of genetic component that copies and pastes itself into other genomic sites by turning RNA back into DNA
10. Person with this syndrome is missing a small region on the long arm of chromosome
15. It is always inherited by the father.
13. A kind of RNA capable of regulating gene expression through the RNA interference phenomenon

**ACROSS**

2. Highly organised complex of DNA and proteins within the nucleus of mammalian cells
5. In this model of 30 nm fibre, the nucleosomal DNA forms a superhelix containing 6 nucleosomes per turn
8. A multiprotein molecular machinery responsible for the replication of DNA
9. Highly variable DNA regions of 1 to 6 nucleotides that can be repeated 10 to 100 times used to determine inheritance patterns
11. An epigenetic modification with acetyl coenzyme A as the donor group
12. Programmed cell death
14. Study of heritable changes that do not affect the DNA sequence but influence gene expression
15. The name given to the progeny of male lion crossed with a female tiger

# SPELLATHON

-Garima and Shreya Kohli
B.Sc.(H) Biochemistry

Arrange the letters given in the puzzle below to make scientific words.

Rules:

- Every word should have at least five letters.
- A letter can be used as many times as it appears in the puzzle.
- Each word must contain the central letter.
- Every letter in the word will give you half a point. Add points of all the words to get your final score.
- A word cannot be repeated by adding a suffix.







Garima, B.Sc. (Hons.) Biochemistry, III Year



(Answers on Pg 48)

# SOLUTIONS

## Quiz Solutions

1. Methylation
2. Father
3. Cytosine
4. 5-Azacitidine
5. Two
6. Gametogenesis
7. Conrad Waddington
8. Cat
9. Dosage Compensation
10. DNA methyltransferase 1 (DNMT1)
11. Angelman syndrome and Prader-Willi syndrome
12. Histone modification, DNA methylation and RNA interference [by small interfering RNA (siRNA) or micro RNA (miRNA)]
13. Chromatin Immunoprecipitation (ChIP)
14. Autoimmune disorders
15. 7 and 11

## Crossword

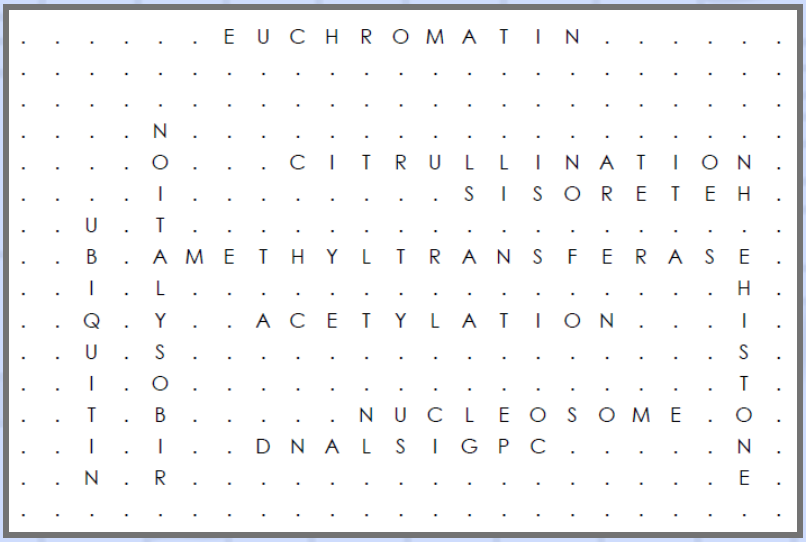
**DOWN**

1. Epistasis
3. Promoter
4. Herbert Spencer
6. Phenocopy
7. Retrotransposon
10. Prader-Willi
13. SiRNA

**ACROSS**

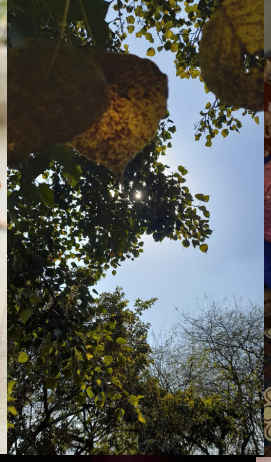
2. Chromatin
5. Solenoid
8. Replisome
9. Microsatellite
11. Acetylation
12. Apoptosis
14. Epigenetics
15. Liger

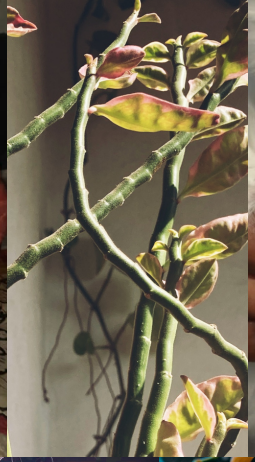
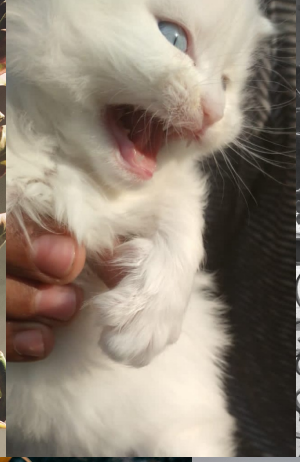
## Word Search

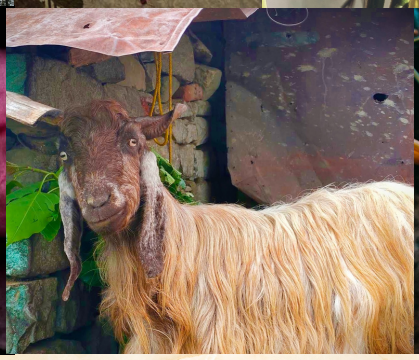



## Spellathon

11 letters - Epigenetics
10 letters - Pestilence
8 letters - Splicing, Pectines, Genetics, Selenite
7 Letters - Splenic
6 Letters - Pectin, Septic, Spleen, Leptin, Lectin, Pistil, Pestle, Ingest
5 Letters - Genes

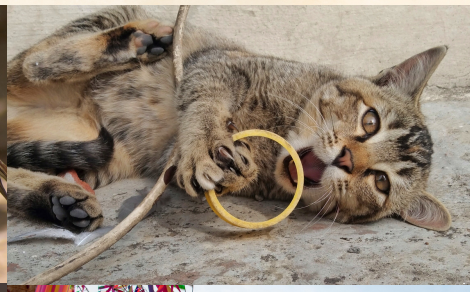
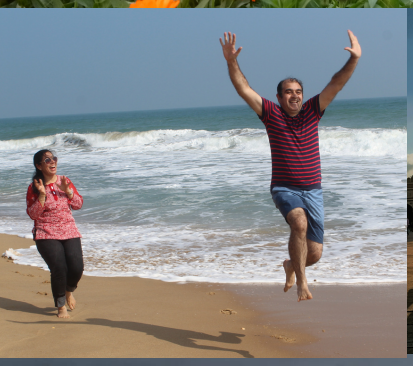



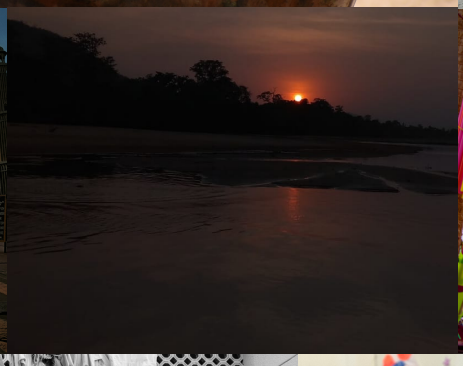


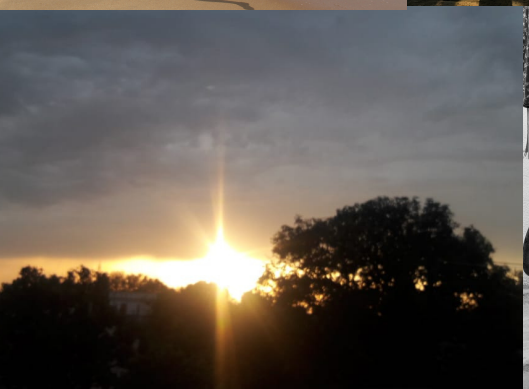
# Image of the Year 2022

## "Made me smile"








# The Winners!

## PICTURES THAT MADE OUR HEARTS SMILE



*"Watching these two playful souls made me smile and capture the moment."*

ISHITA SEHGAL,
BIOCHEMISTRY, THIRD YEAR

*"Kasol, a popular destination in Himachal mothered by the Parvati valley. It is known for its scenic beauty, thrilling treks, flavoursome food, roaring river and heartfelt humanity."*



ADITI GUPTA,
BIOCHEMISTRY, FIRST YEAR



*"Smile at strangers and it might just change a life"*
*The reality is that wealth tends to change our focus. When you have money, life seems to center on what it can buy, what it can do, and how to get more of it. We lose simplicity in our lives.*
*The children in this picture, sitting peacefully, enjoying each other's company, away from all worldly deeds, does make me smile. The innocence and simplicity on their faces is enough to brighten up my day :)*

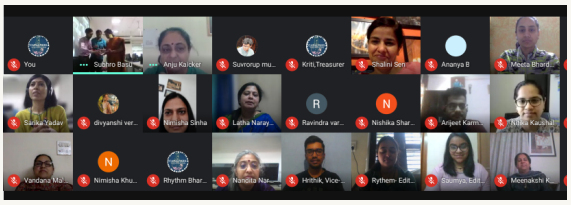
PRIYAL VERMA,
B.A. PROGRAMME, FIRST YEAR

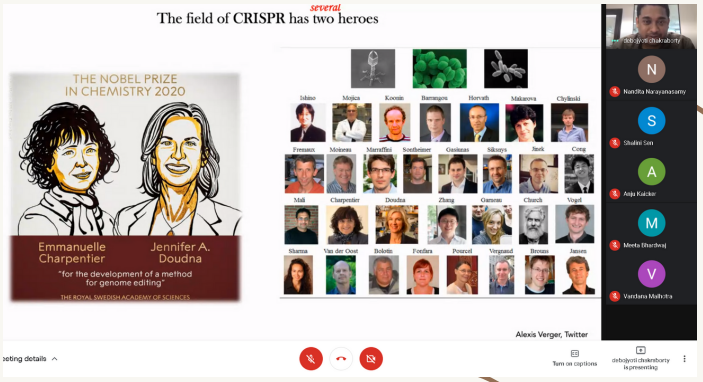
# Picture Studio - Every picture tells

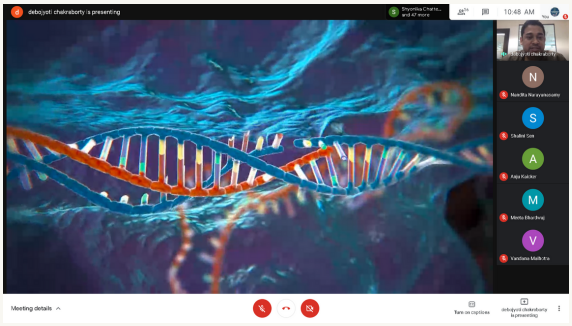
## Amalgam & Magazine Launch '21

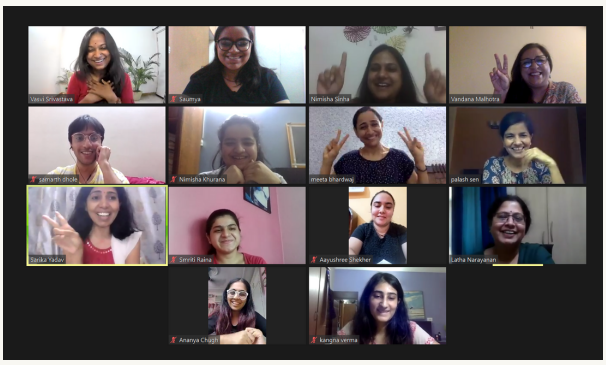




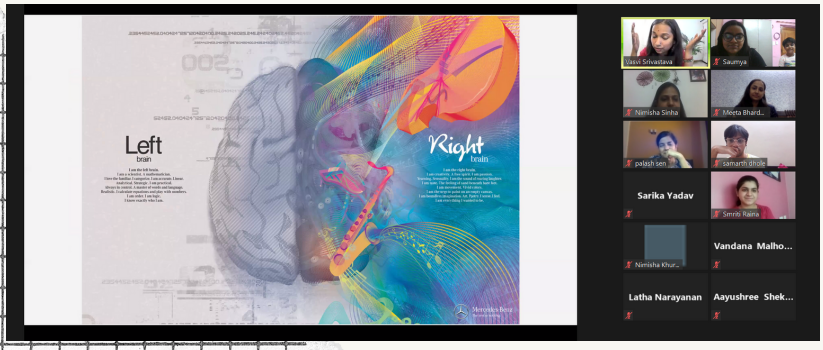









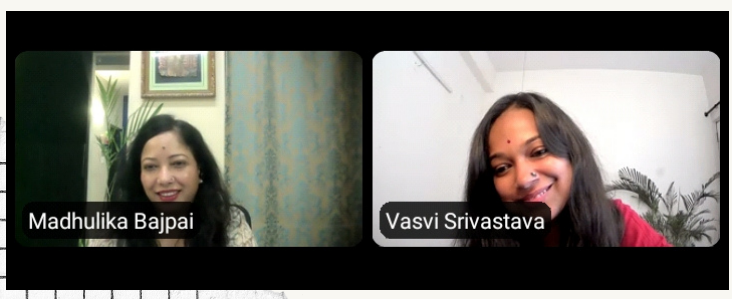












## Realize, Reflect & Reach out
## A Workshop

# a story, every story needs a picture



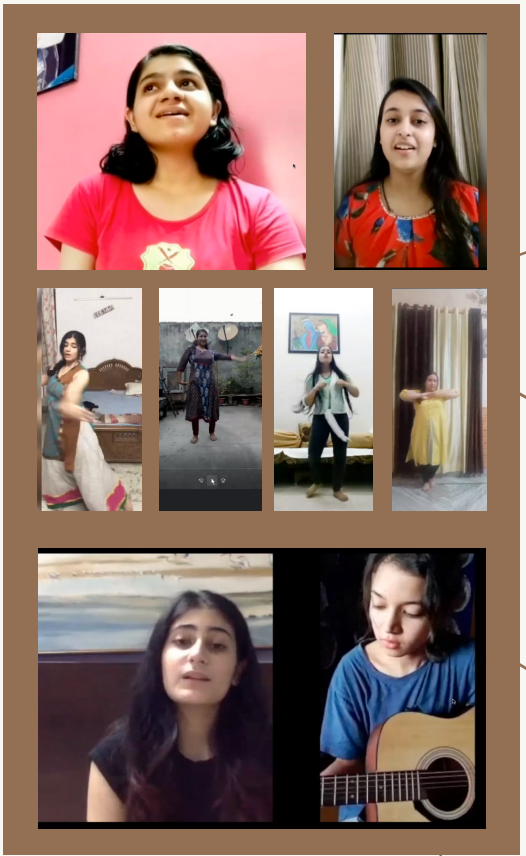


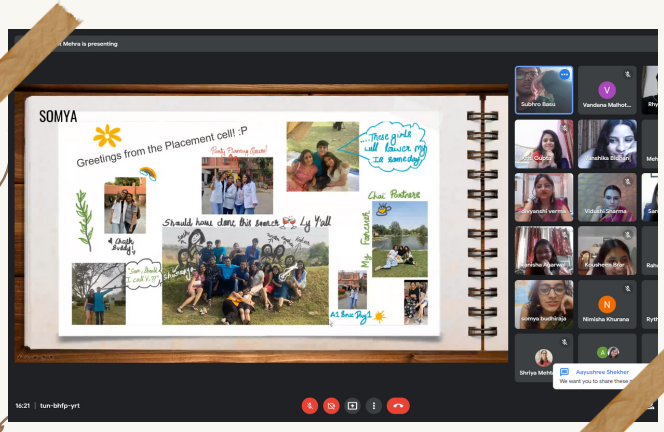


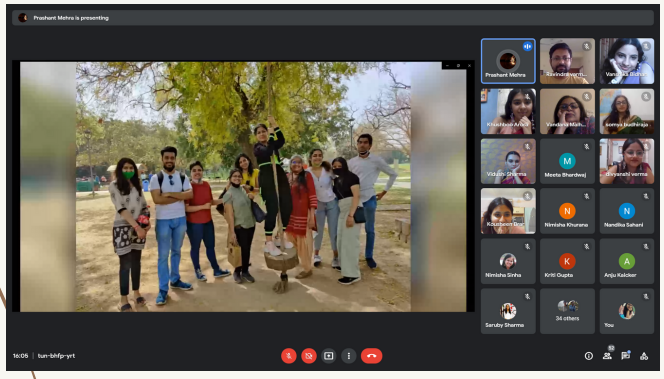


## Farewell











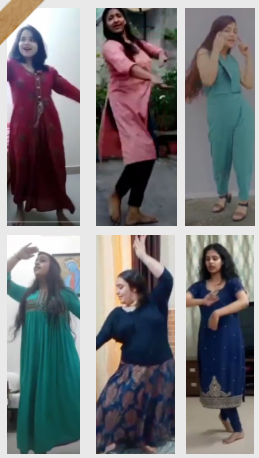

*When they hand you your degree, keep moving..just in case they try to take it back!*

# Teacher's Day Celebration

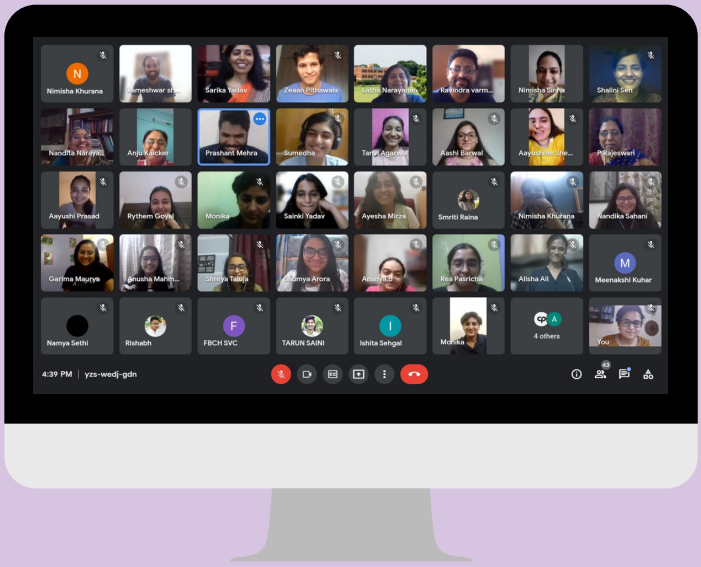






Performances





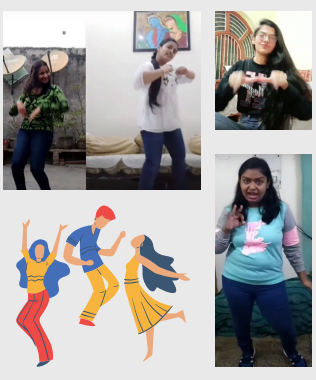



# Freshers '21

FBCH







# Research Laboratory Inauguration

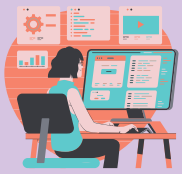




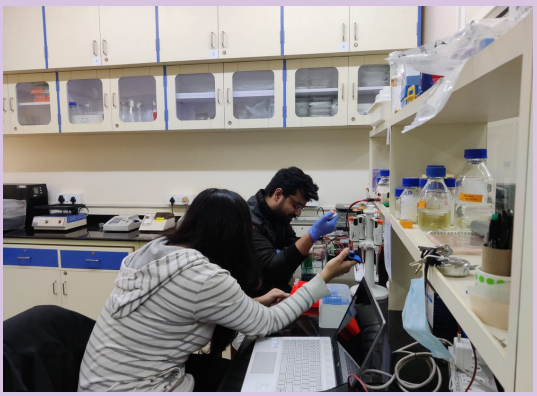






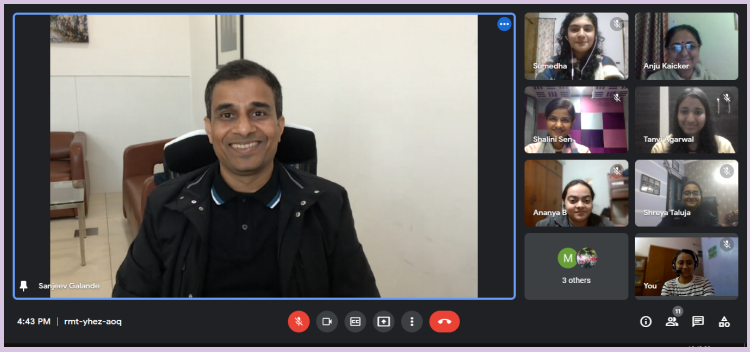







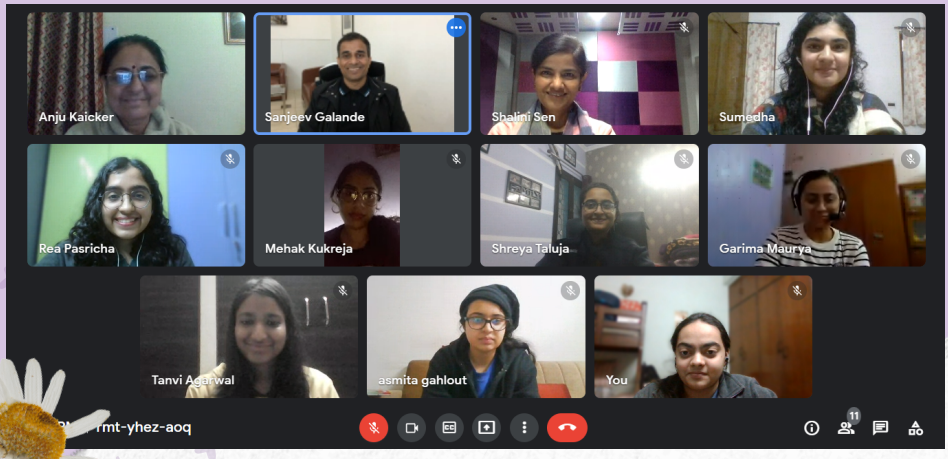


Interview with Dr. Sanjeev Galande



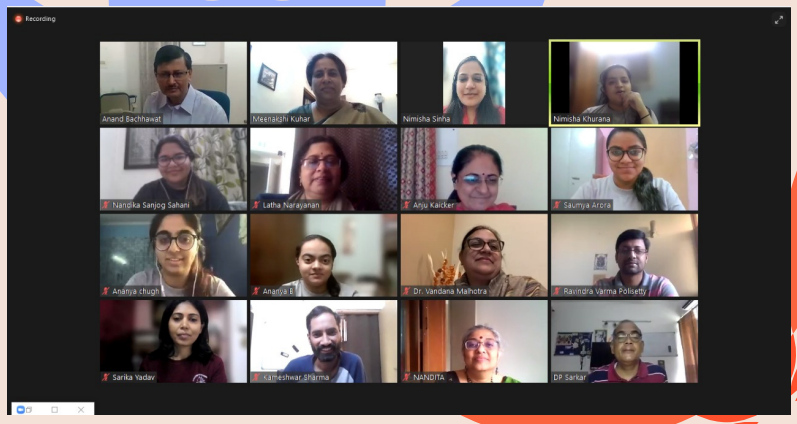






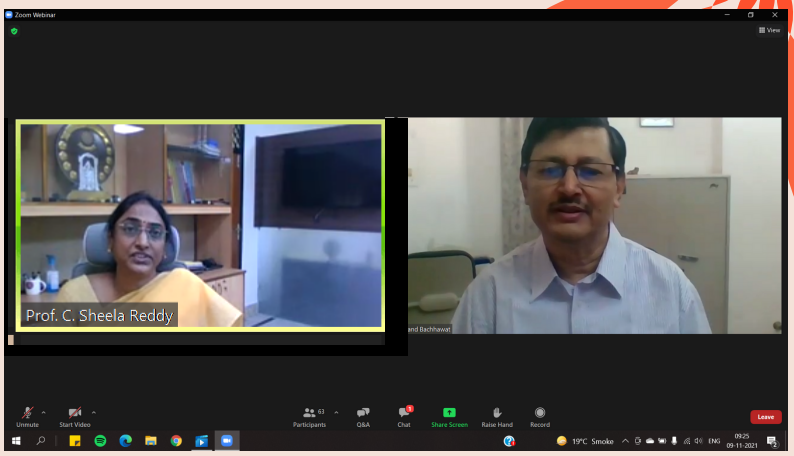


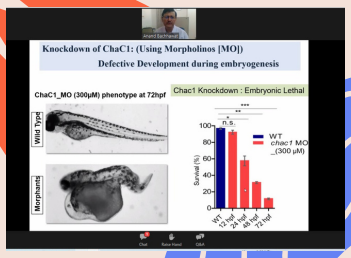

# Webinar - Prof. B.K. Bachhawat

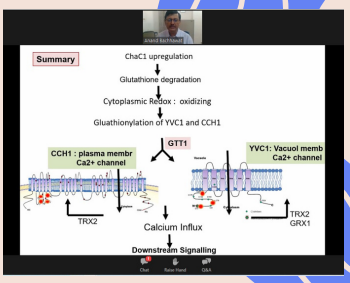


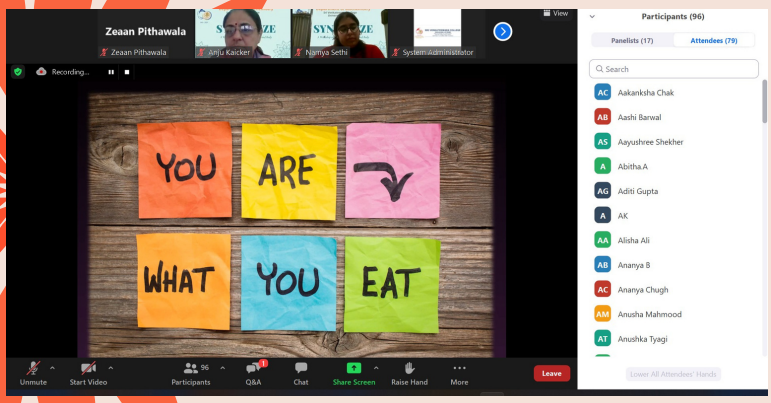






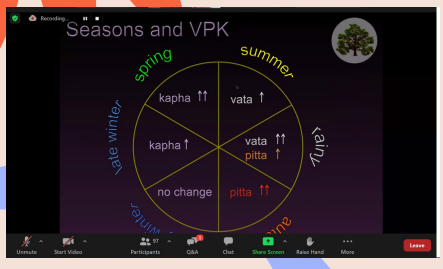



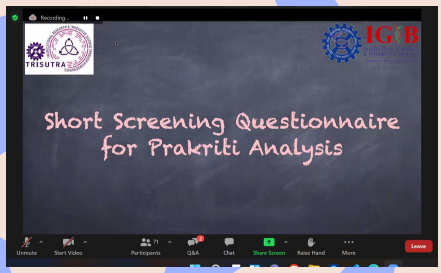


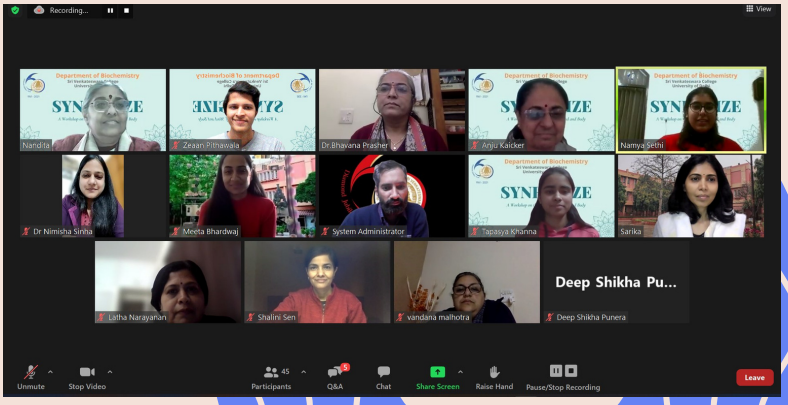









# Synerjize - A Workshop on wellness of mind and body

Tough times don't last but tough teams do!



Catalysis Team!



Editorial Board



Amalgam Team



Wall Magazine Team

# CLASS OF 2022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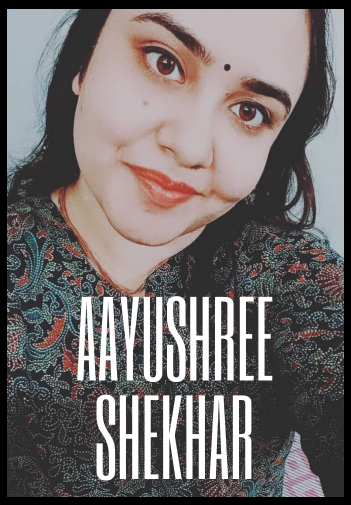
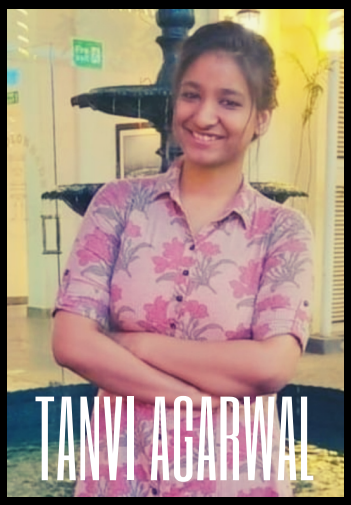
ANANYA KUMAR


SMRITI RAINA


AAYUSHREE SHEKHAR


TANVI AGARWAL


KESHAV RAJESH


NIMISHA KHURANA


PRASHANT MEHRA


NAMYA SETHI


ISHITA SEHGAL


ANSHUL UPADHYAY


GARIMA


NANDIKA SAHANI


SAUMYA ARORA

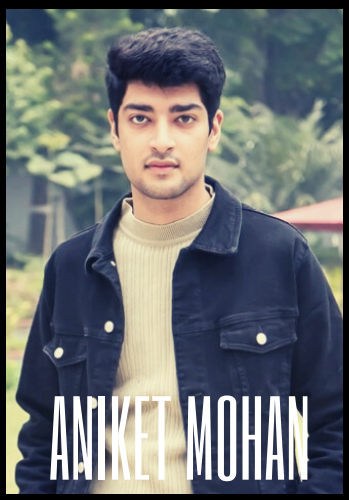

ANANYA
BANDYOPADHYAY


VINITA KHOKHAR


RIYA SAH


RADHIKA SINGH

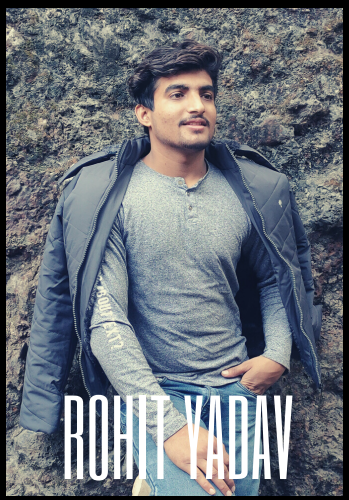

TARUN SAINI


ANIKET MOHAN


MEHAK KUKREJA


KANGNA VERMA


AYESHA MIRZA


ROHIT YADAV

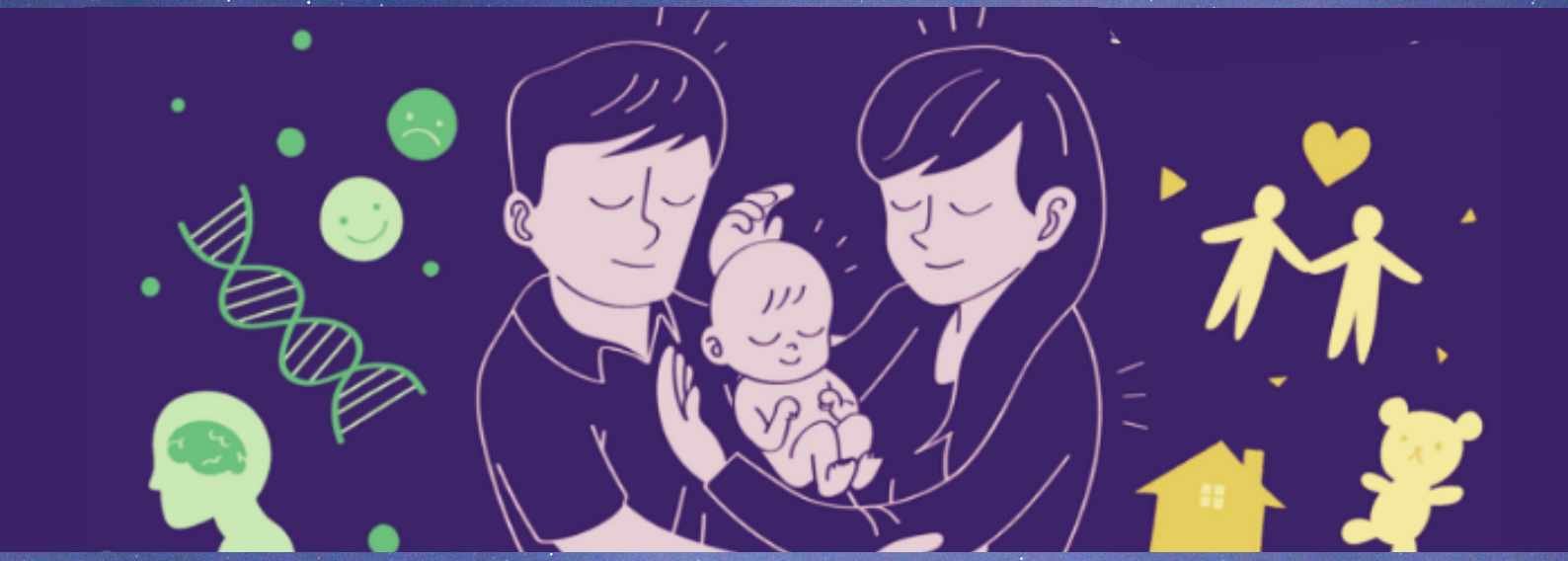

ANANYA CHUGH


ASMITA GAHLOT


BIPASHA YADAV


MEENAKSHI
SHARMA

AU REVOIR!



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