Epigenetic Influences on Mental Health

PROF. DR. PARIN SOMANI
Director, Department of Skill Development, London Organisation of Skills Development Ltd, London, United Kingdom

Abstract- ***A significant number of difficulties that are associated with one's mental health might have origins that can be traced back to childhood. Gaining an understanding of the processes that explain how psychosocial experiences are physically imprinted and how they effect lifelong development is the primary challenge that faces the several mental health professions today. In recent years, epigenetic processes have come to the forefront as a probable mechanism that can regulate the long-term sensitivity that might be a direct result of having experienced trauma. This has been the case since epigenetic processes have been linked to a number of diseases, including cancer and Alzheimer's disease. Animal models provide evidence to support the notion that early-life trauma can create lasting epigenetic modifications in the brain, which drive disorder-like behaviour.***

Indexed Terms- ***Mental Health, Mechanisms, Environmental***

I. INTRODUCTION

It has been shown that those who have outstanding mental health have a broad diversity of epigenetic changes, in contrast to individuals who suffer from psychiatric issues.5,16,17 Although there are a great number of possible explanations for these variances, some of them are thought to be influenced by the environment that surrounds them, and they may act as a buffer against the effect that following stress has on mental health.18 As was previously said, the mechanisms of epigenetics have the ability to make a lasting record of exposure to a broad variety of different life experiences. The great majority of research that have been conducted on epigenetics in the field of psychiatry up until this point have investigated the impact of singularly negative experiences on the epigenome as well as the ways in which unique genetic variants contribute to the development of a single ailment.[1] There are other reviews that cover this topic, which connects the dots.7,17-19 However, there is still a lack of understanding about the function that protective and positive environmental variables have in affecting epigenetics and, as a result, contributing to the development of psychological resilience. Despite the fact that they have the ability to dramatically impact findings, genetic variation and the genetic moderation of environmental impacts on epigenetics are generally ignored in research. [2] This is of the utmost relevance due to the fact that individuals exhibit such a broad range of susceptibility to both risk and protection.20

As a consequence of this, we provide a conceptual model for three unique functions of epigenetics in the development of psychological resilience throughout the course of a person's lifetime. This model is based on the research that has been conducted on the relationships between the experience of adversity, epigenetics, and psychological consequences. Our conceptual representation of the model is shown in Figure 1. [3] The essential proposition of this paradigm is that being confronted with adversity (2) paves the way for resilience (3), which ultimately results in good multidimensional mental health (1). Epigenetics can influence the robust outcome in at least three different ways, all of which take place during an individual's lifetime (3). To begin, some degree of an epigenetic imprint of resilience may already be present at the time of conception, either as a consequence of a direct inheritance (4b) or as a result of genetic variation (4a). This may be the case. Second, the surrounding environment has the potential to change a number of components of an individual's epigenome, particularly in the first few years of a person's existence (5). Finally, the availability of specific protective factors throughout the period of exposure to adversity determines the degree to which the epigenome is vulnerable to the occurrence of this harmful event (6). Last but not least, genetic factors also play an important part, having a direct influence on the capacity for resistance (7a) and helping to mitigate the effects of the environment on the epigenome (7b). It is very necessary to investigate each of these facets in order

to acquire an understanding of the myriad of possible ways in which epigenetic variables contribute to resilience. In the following part of this review, we will discuss in greater depth the study that was conducted on each individual part of this model.[4]

It has been shown that those who have outstanding mental health have a broad diversity of epigenetic changes, in contrast to individuals who suffer from psychiatric issues.5,16,17 Although there are a great number of possible explanations for these variances, some of them are thought to be influenced by the environment that surrounds them, and they may act as a buffer against the effect that following stress has on mental health.18 As was previously said, the mechanisms of epigenetics have the ability to make a lasting record of exposure to a broad variety of different life experiences. The great majority of research that have been conducted on epigenetics in the field of psychiatry up until this point have investigated the impact of singularly negative experiences on the epigenome as well as the ways in which unique genetic variants contribute to the development of a single ailment. [5] There are other reviews that cover this topic, which connects the dots.7,17-19 However, there is still a lack of understanding about the function that protective and positive environmental variables have in affecting epigenetics and, as a result, contributing to the development of psychological resilience. Despite the fact that they have the ability to dramatically impact findings, genetic variation and the genetic moderation of environmental impacts on epigenetics are generally ignored in research. This is of the utmost relevance due to the fact that individuals exhibit such a broad range of susceptibility to both risk and protection.[6]

As a consequence of this, we provide a conceptual model for three unique functions of epigenetics in the development of psychological resilience throughout the course of a person's lifetime. This model is based on the research that has been conducted on the relationships between the experience of adversity, epigenetics, and psychological consequences. Our conceptual representation of the model is shown in Figure 1. [7] The essential proposition of this paradigm is that being confronted with adversity (2) paves the way for resilience (3), which ultimately results in good multidimensional mental health (1). Epigenetics can influence the robust outcome in at least three different ways, all of which take place during an individual's lifetime (3). To begin, some degree of an epigenetic imprint of resilience may already be present at the time of conception, either as a consequence of a direct inheritance (4b) or as a result of genetic variation (4a). This may be the case. Second, the surrounding environment has the potential to change a number of components of an individual's epigenome, particularly in the first few years of a person's existence (5). Finally, the availability of specific protective factors throughout the period of exposure to adversity determines the degree to which the epigenome is vulnerable to the occurrence of this harmful event (6). Last but not least, genetic factors also play an important part, having a direct influence on the capacity for resistance (7a) and helping to mitigate the effects of the environment on the epigenome (7b). It is very necessary to investigate each of these facets in order to acquire an understanding of the myriad of possible ways in which epigenetic variables contribute to resilience. In the following part of this review, we will discuss in greater depth the study that was conducted on each individual part of this model.

- Genetic mapping studies of mental disorders

Over the past several decades, there has been a significant rise in the number of people working to sequence the genes that are responsible for mental diseases. Studies of linkage and association have been the primary methods utilised in this endeavour to pinpoint the genes that are responsible for these disorders. Investigation of the role that genes have in the development of mental illnesses The origins of neuropsychiatric conditions such as Alzheimer's disease, fragile X syndrome, Rett syndrome, and Huntington's disease have all been linked back to certain mutations and polymorphisms in genes. Molecular genetic testing may be used to identify the latter two disorders, both of which have been associated to an increase in trinucleotide repeats and can be diagnosed. [8]

- *Genetic mapping studies of idiopathic mental disorders*

Studies of linkage and association have been done with a significant amount of effort in attempt to locate the genes that are responsible for idiopathic mental diseases.[9] Inconclusive findings have been found so far in research on the genetic basis of

mental illnesses such as schizophrenia, bipolar disorder, and major depressive disorder. The failure of genetic mapping studies to identify the genes that underlie idiopathic mental disorders has been attributed to a wide variety of factors, such as polygenic and multifactorial causation, gene-environment interactions, genetic heterogeneity, small population-wide effects of individual susceptibility genes, epistasis, differences in statistical strategies and ethnic differences across the studies, genotyping and diagnostic errors, and errors in idiopathic mental disorders. The hypothesis of these research, which states that idiopathic mental disorders are caused by genetic changes or polymorphisms, has been put into doubt as a result of these findings. It has been hypothesised that epimutations and epigenetic polymorphisms, neither of which change the sequence of the DNA, are rather at the foundation of the genetic basis. [10]

- *Mitochondrial DNA and the Risk of Developing a Mental Disorder*

The role that mitochondrial genes have in the development of mental illnesses is another topic that has been investigated18. In spite of the fact that mutations in mitochondrial genes cause mental difficulties due to diseases of the brain such as encephalopathy and Alzheimer's disease, which are attributed to normal ageing and the degenerative brain disease, this gene has not been conclusively proven to be the cause of idiopathic mental states.

- *Molecular aspects of Epigenetics*

Epigenetics is the study of heritable changes in gene expression that occur without a change in the DNA sequence. At the core of epigenetics is the study of heritable modifications in gene expression. Epimutations are a type of genetic abnormality that is passed down through families and affects gene expression but does not alter the DNA sequence. Both epigenetic polymorphisms, which may be defined as differences in epigenetic patterns across people, and epialleles, which are epigenetic variations of a genetic allele, are related concepts. Epigenetic polymorphisms have been described as changes in epigenetic patterns between individuals. For example, DNA methylation polymorphisms are differences in the patterns of DNA methylation that are found everywhere across the genome.[11]

Our comprehension of the molecular mechanisms behind epigenetics is advancing at a breakneck pace. It has been demonstrated that the interaction of these three distinct molecular processes is what causes this phenomena to take place. RNA polymerase II is responsible for the regulation of the methylation cycle. In the presence of cytosine in DNA, the carbon-5 position of cytosine undergoes modification by the enzymatic addition of a methyl group. Sadenosylmethionine serves as the source of the methyl group in this process. This takes place at sites where cytosine is present. The majority of the 5'-methylcytosine found in mammalian DNA is found in the 5'-CpG-3' dinucleotides. Although the frequency of methylation in non-CpG sequences is often considerably lower, they are not immune to it. Within the human genome, the methylation of CpG sites is controlled by a group of enzymes known as DNA methyltransferases (DNMTs), of which there are four well-studied examples. Two of the DNMTs are designated as DNMT1 and DNMT2, while the remaining four are designated as DNMT3A and DNMT3B. DNA methylation serves a wide variety of purposes, some of which include the elimination of transposable elements, the prevention of damage caused by viral sequences, and the regulation of the transcription of particular genes. When eukaryotic DNA is strongly attached to the proteins that make up the cell, it transforms into a DNA-protein complex that is referred to as chromatin29. This whole construction is really organised and compact. The little, important proteins known as histones make up virtually all of the chromatin's protein content. Histones are a category of proteins. The histone tail domains can be modified by acetylation, methylation, and phosphorylation. These are all examples of histone modifications. The change in chromatin structure that this process produces ultimately determines how genes are expressed.[12] There is some evidence that changes to histones can act as a dynamic on/off switch for gene expression. Differences in histone modification create open euchromatic (on) or closed heterochromatic (off) states29, which are responsible for this "on-off" transcriptional regulation. Recent research has uncovered yet another epigenetic mechanism (30) that is involved in the process of gene expression. This approach makes use of short RNAs, which have the capacity to silence genes throughout the transcription process as well as after it has completed. These RNAs are produced as a byproduct of the cleavage of double-stranded RNA. Tiny RNAs include things like micro RNAs (also known as miRNAs) and small interfering RNAs (also known as siRNAs).[13] The silencing of genes

by RNA is a crucial mechanism for the regulation of genes, the preservation of chromosomal structure, and the defence of the genome.

- *Environmental and stochastic factors involved in epigenetics, normal behaviour and mental disorders*

It is believed that epigenetic processes work as a bridge between genes and the environment in common illnesses, which involve interactions between the two 31. There is evidence that interactions between genes and the environment play a part in the development of many prevalent diseases. The mechanisms of epigenetics that govern gene expression are extremely vulnerable to the effects of environmental factors. Because the amount of methionine in the diet affects the methylation of DNA34, consuming a high quantity of the metabolic precursor of sadenosylmethionine while pregnant and in the first few years after giving birth may increase the likelihood that you will acquire a chronic disease in later life. This is because sadenosylmethionine uses dietary methionine as a metabolic precursor. The reason for this may be found in the fact that. Proteins that are susceptible to influence from their environment include enzymes with roles in DNA methylation and histone modification, to name just two examples. Through the use of epigenetic processes, some proteins, such as polycomb proteins, play the role of mediators between the environment and the expression of genes. Polycomb proteins are a type of protein that maintain a repressed state for a large number of genes that are essential for normal development. [14]

Experimental data has been gleaned from studies conducted with animals, suggesting that psychological effects may be able to modify behaviour via epigenetic mechanisms. There is accumulating data that points to psychosocial factors in the environment as major contributors to the genesis of idiopathic mental diseases in individuals. Experiments using cross-fostering in rats, for example, have demonstrated that maternal behaviour and stress reactions may be passed down from one generation to the next in a manner that is not inherited genetically. It is feasible for these responses to be passed on from mother to child in some cases. Researchers were able to demonstrate, through the use of two independent lines of inbred mice, that prenatal and postnatal environmental influences, as opposed to inherited genetic variations, may be responsible for strain-related behavioural abnormalities. Researchers examined the effects of maternal licking and grooming on rat pups and discovered that more frequent maternal behaviour resulted in more hippocampal glucocorticoid receptors and better control of glucocorticoid production.[15] This was discovered after the researchers analysed the effects of maternal licking and grooming on rat pups. Changes in DNA methylation and histone acetylation linked with the glucocorticoid receptor gene promoter were the cause of the higher levels of glucocorticoid receptors seen in the pups. These changes were caused by exposure to an environmental factor. These disparities became apparent during the second week of the newborn baby's life, vanished after the infant experienced cross-fostering, but remained until the child reached maturity. Random or stochastic factors are thought to have a role in epigenetics, according to one popular theory. As a result, it is conceivable that uncontrollable events might play a part in the epigenetic modifications that produce psychiatric diseases. Recent experimental research has demonstrated that the expression of genes in animals may be altered by a wide range of variables, including the environment, the randomness of events, epigenetics, and genetics itself.

II. OBJECTIVE OF THE STUDY

1. To study on epigenetics affects mental health is one objective.
2. To determine whether or not genes found in mitochondria play a part in the development of mental disorders.

- *Scope for epigenetics in mental disorders*

Because the genetic information contained in the human genome is insufficient to specify all of the neuronal interconnections in the human brain, the development of the human brain requires additional information in the form of epigenetics.[16] This is a branch of genetics in which specific genes contained within brain cells are activated and modulated during the course of development. Epigenetics is required because the human genome does not contain enough information. Epigenetic mechanisms in gene expression have been implicated as a possible factor in the development of mental illnesses, and several lines of evidence point in this direction. It is believed that epigenetics had a

significant part in the development of human cognitive capacities during the course of human evolution. Many people believe that the development of the brain can benefit the most from epigenetic modification, especially when compared to the development of other organs. Epigenetics, which uses environmental inputs in gene expression but may not entail changes to the DNA sequence, may be able to explain many of the clinical aspects of idiopathic mental disorders15. Epigenetics uses environmental inputs in gene expression.[17] These characteristics include a high degree of discordance among monozygotic twins for these disorders, a relatively late age at which they first appear, differences between the sexes in the rate and course of illness, fluctuations in the course of illness, and the presence of a parent of, or sibling of, or child of, or child of a person who has the disorder. For instance, several clinical and molecular studies have demonstrated that chromosomes are connected with parent-of-origin effects in the condition known as bipolar illness.

Genomic imprinting is frequently to blame for what are known as parent-of-origin effects. The fundamental mechanism behind genomic imprinting is called differential epigenetic alteration of genes according to parental origin15. Methods based on epigenetics are being used to locate the genes responsible for idiopathic mental illnesses.[18] The approaches of epigenetics are discussed in this article. If these procedures are effective, they may lead to the discovery of the genes responsible for idiopathic psychiatric illnesses. Examining postmortem brain tissue or leucocytes from people who have these disorders for changes in DNA methylation and chromatin remodelling is one approach. The sequencing of the genome is yet another approach that may be taken. It is difficult to research how histones are transformed because chromatin is changed during long-term preservation of postmortem brains. This makes it tough to study. In addition, these investigations need a substantial amount of human work, and they provide a significant amount of difficulty when it comes to the interpretation of the data. Because brain tissues are the place where the disease first appears and where it progresses, they are of special interest in this context. Recent paradigm developments in the technology used to profile DNA have led to a significant rise in the practise of methylation profiling. A additional epigenetic approach for identifying the genes responsible for idiopathic mental disorders is the identification of aberrant gene expression patterns in the postmortem brain tissue of individuals who have suffered from these problems. This is an epigenetic method that uses postmortem brain tissue of individuals who have died from these ailments. [19]

III. PEEDICAYIL: EPIGENETICS IN MENTAL DISORDERS

In order for these studies to be successful, researchers will need to address a number of challenges, including the difficulty of distinguishing changes in gene expression brought on by sickness from experimental noise and the absence of a relationship between variations in gene expression and alterations in protein levels inside individual neurons. It's possible that these patterns will shed light on how epigenetic processes affect underlying gene expression47. Molecular evidence demonstrating that epigenetic pathways have a role in the development of mental diseases Studies at the molecular level on epigenetic pathways in patients diagnosed with idiopathic mental illnesses are only getting started. Petronis and colleagues looked at the methylation patterns of DNA isolated from lymphocytes in the 5' regulatory region of the dopamine D2 receptor gene in a research that included a total of fifty people, including two sets of monozygotic twins. There found some duplication in both sets, but only one of them was consistent with schizophrenia. Within each monozygotic twin pair and between monozygotic twin pairs in the area that was investigated, many DNA methylation variations were discovered. The affected twin from a pair of discordant twins for schizophrenia was more genetically related to his affected concordant twins than he was to his unaffected monozygotic twin who had the monozygotic form of the disorder. In a different study (51), the promoter methylation of the RELN gene, which codes for the protein reelin, was studied in the frontal lobes of the brains of 10 schizophrenia patients. It was demonstrated that this gene had a high level of methylation, which led to a reduction in the amount of expression it had. In order to conduct an investigation on the methylation levels inside the CpG island of the RELN promoter, genomic DNA was taken from the cerebral cortex of 30 people who had schizophrenia and 30 people who did not have the disorder. According to the findings of the inquiry, all of the individuals' blood methylation levels fell within the

parameters of what is considered to be normal. The methylation of this promoter region was demonstrated to be responsible for the decreased reelin expression that was observed in schizophrenia patients. Iwamoto et al.53 discovered an increase in the amount of DNA that was methylated in the oligodendrocyte-related gene SOX10 in the postmortem brains of patients who had schizophrenia. Gene expression is inhibited to this degree whenever DNA is methylation to such a degree. In a different study54, high amounts of the amino acid H3- (methyl) arginine 17 were found in the prefrontal cortex of 8 out of 41 patients diagnosed with schizophrenia. The expression of four metabolic genes was inhibited as a consequence of these higher levels.[20]

The gene expression of the 41 patients was not significantly different from normal when compared to the histone patterns of the matched controls, and there were no anomalies in the gene expression of the patients. Idiopathic mental diseases have also been shown to have evidence of aberrant epigenetic pathways. These pathways are involved in the expression of genes and have a part in the process. In the temporal cortex of dead patients with schizophrenia, changes in the expression of a large number of genes, including the encodin histone deacetylase 3 gene55, have been discovered. Downregulation of the gene that codes for 67-kDa glutamic acid (GAD67) and the RELN gene has been seen in studies of GABAergic interneurons in the postmortem prefrontal cortex of individuals with schizophrenia (56,57). This downregulation was shown at both the transcriptional and translational stages. Both genes were found in the GABAergic interneurons that harboured them.

These alterations were observed in psychotic patients but not in depressed patients who did not have psychosis 58. Depressive individuals who did not have psychosis 58 did not display these changes. Overexpression of DNA methyltransferase-1 (DNMT1) in these neurons has been associated to the changes that have been described59,60. In the brains of mice that were given methionine for an extended period of time (6.6 mmol/kg twice a day for 15 days), hypermethylation of the promoter regions of the reelin and GAD67 genes led to a decrease in their transcription61. These findings in human subjects are in agreement with those obtained from animals. It has been shown, as was said before, that some genetic mutations and polymorphisms are connected to neuropsychiatric illnesses. These connections were uncovered via research. These variations in genetic material, such as mutations and polymorphisms, have the potential to be modified by epigenetic means. As a result, mutations in the MeCP2 gene, which are responsible for the production of the MeCP26 protein, are the most common cause of Rett syndrome. MeCP2 holds a unique position among the group of proteins that are collectively referred to as methyl-CpGbinding proteins. Around seventy distinct amino acids are included of the methyl-CpG-binding domain that is found in each of these proteins. The regulation of gene transcription by these proteins may be accomplished through the use of epigenetic processes, as this concept proposes. [21]

The FMR1 gene on the X chromosome is silenced transcriptionally when the number of CGG repeats in the 5' untranslated region of the gene accumulates to more than 200. This causes the repeat to become hypermethylated and results in the gene being silenced. In around 90 percent of cases of fragile X, a condition known as fragile X manifests itself.[22] Histones of people diagnosed with fragile X syndrome have reportedly been shown to be abnormal. There is some evidence to support the hypothesis that epigenetic processes play a part in the aetiology of Alzheimer's disease. However, there is not enough data to definitely conclude whether or not epigenetic processes play a function in the aetiology of Alzheimer's disease. An inverse association between age and methylatio was identified by a study that employed bisulphite sequencing to investigate methylation status in a CpG region of the amyloid precursor protein (APP) gene in human postmortem cerebral cortices. As a result, the researchers found that methylation levels decreased with increasing age.[23]

In addition, hypomethylation64 of the APP gene was identified in the brain genomic DNA of patients with Alzheimer's disease. Epigenetics' potential use in clinical settings for the treatment of mental illnesses There is just a scattering of evidence available at this time about the impact that epigenetics plays in the beginning stages of idiopathic mental diseases. On the other hand, it is anticipated that epigenetics will play a role in the management of these ailments in the not-too-distant future, therefore presenting new

options for the diagnosis and treatment of these conditions.[24]

In the not-too-distant future, one of the primary focuses will be on enhancing our comprehension of the dynamic interactions that take place between the environment, epigenetic processes, and gene expression as they pertain to the aetiology of illness. Epigenetic treatment is a relatively new sort of therapeutic alternative that might be beneficial to patients who suffer from idiopathic mental problems. Inhibitors of histone deacetylation or DNA methylation, which both change methylation patterns, may be included in the medication that is administered during epigenetic treatment. Both in preclinical and clinical research settings, an increasing number of these medications are being investigated for use in areas that are not traditionally associated with psychiatry. It is probable that epigenetic pathways are somewhat responsible for the success that valproic acid and its salt, sodium valproate, have had in the treatment of bipolar disease during the past few decades. This notion came forth as a result of the observation that the chemical structures of valproic acid and sodium valproate are fairly comparable to one another. The importance of epigenetic variables in neuropsychiatric illnesses has long been recognised, which lends credence to the possibility that treatments based on epigenetics might be useful in the treatment and management of these conditions. The use of epigenetic treatment comes with the risk of causing cancer as a side effect, in addition to the potential for the unintended activation of genes within cells.

CONCLUSION

The field of research known as epigenetics focuses on the changes that may be made to gene expression without affecting the DNA sequence itself. The years have brought about a significant sea change in people's perspectives on the counselling profession. The purpose of this essay is to educate counsellor educators and counselling practitioners on the possible impact that epigenetics plays in mental health. Recent studies in the field of epigenetics of mental health have shown evidence that traumatic psychosocial events are connected with schizophrenia, anxiety, depression, and addiction. These studies were conducted in the United States. Counselling practises, such as cognitive behavioural therapy, mindfulness, healthy eating, and physical exercise, have been related to having a positive epigenetic effect, as has the practise of eating healthfully.

REFERENCES

[1] Sadock BJ, Sadock VA. Kaplan & Sadocks' synopsis of psychiatry. Philadelphia: Lippincott Williams & Wilkins; 2003 p. 170-7, 329-45, 1161-79.
[2] Margolis RL, McInnis MG, Rosenblatt A, Ross CA. Trinucleotide repeat expansion and neuropsychiatric disease. Arch Gen Psychiatry 1999; 56 : 1019-31.
[3] Thapar A, McGuffin P. The contribution of genetics: Quantitative genetics. In: Gelder MG, López - Ibor JJ, Andreasen NC, editors. New oxford textbook of psychiatry. Oxford: Oxford University Press; 2000 p. 233-42.
[4] Baron M. The search for complex disease genes: fault by linkage or fault by association? Mol Psychiatry 2001; 6 : 143-9.
[5] Cacabelos R. The application of functional genomics to Alzheimer's disease. Pharmacogenomics 2003; 4 : 597-621.
[6] Caballero IM, Hendrich B. MeCP2 in neurons: closing in on the causes of Rett syndrome. Hum Mol Genet 2005; 14 : R19-26.
[7] Allen EG, He W, Yadav-Shah M, Sherman SL. A study of the distributional characteristics of FMR1 transcript levels in 238 individuals. Hum Genet 2004; 114 : 439-47.
[8] Ropper AH, Brown RH. Adams and Victor's principles of neurology. New York: McGraw - Hill; 2005 p. 850-94; 895-8.
[9] Riley B, Kendler KS. Molecular genetic studies of schizophrenia. Eur J Hum Genet 2006; 14 : 669-80.
[10] Potash JB. Carving chaos: genetics and the classification of mood and psychotic syndromes. Harv Rev Psychiatry 2006; 14 : 47-63.
[11] Levinson DF. The genetics of depression : A review. Biol Psychiatry 2006; 60 : 84-92.
[12] Barondes SH. An agenda for psychiatric genetics. Arch Gen Psychiatry 1999; 56 : 549-52.
[13] Owen MJ, Cardno AG, O'Donovan MC. Psychiatric genetics: back to the future. Mol Psychiatry 2000; 5 : 22-31.

[14] Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, Part II: Schizophrenia. Am J Hum Genet 2003; 73 : 34-48.
[15] Petronis A. Human morbid genetics revisited: relevance of epigenetics. Trends Genet 2001; 17 : 142-6.
[16] Peedicayil J. The importance of cultural inheritance in psychiatric genetics. Med Hypotheses 2002; 58 : 164-6.
[17] Crow T. Genes for schizophrenia. Lancet 2003; 361 : 1829.
[18] Kato T. The other, forgotten genome: mitochondrial DNA and mental disorders. Mol Psychiatry 2001; 6 : 625-33.
[19] Chinnery PF, Schon EA. Mitochondria. J Neurol Neurosurg Psychiatry 2003; 74 : 1188-99.
[20] Kakiuchi C, Ishiwata M, Kametani M, Nelson C, Iwamoto K, Kato T. Quantitative analysis of mitochondrial DNA deletions in the brains of patients with bipolar disorder and schizophrenia. Int J Neuropsychopharmacol 2005; 8 : 515-22.
[21] Wolffe AP, Matzke MA. Epigenetics: Regulation through repression. Science 1999; 286 : 481-6.
[22] Numachi, Y., Yoshida, S., Yamashita, M., Fujiyama, K., Naka, M., Matsuoka, H., Sato, M., & Sora, I. (2004). Psychostimulant alters expression of DNA methlytransferase mRNA in the rat brain. Annals of the New York Academy of Sciences, 1025(1), 102–109.
[23] https://doi.org/10.1196/annals.1316.013 Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008).
[24] Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics, 3(2), 97–106. https://doi.org/10.4161/epi.3.2.6034
[25] Okazaki, S., Otsuka, I., Numata, S., Horai, T., Mouri, K., Boku, S., Ohmori, T., Sora, I., & Hishimoto, A. (2019). Epigenetic clock analysis of blood samples from Japanese schizophrenia patients. npj Schizophrenia, 5(9), 1–7. https://doi.org/10.1038/s41537-019-0072-1
[26] Ouellet-Morin, I., Wong, C. C. Y., Danese, A., Pariante, C. M., Papadopoulos, A. S., Mill, J., & Arseneault, L. (2013). Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: A longitudinal study of discordant monozygotic twins. Psychology of Medicine, 43(9), 1813–1823. https://doi.org/10.107/S0033291712002784
[27] Palmisano, M., & Pandey, S. C. (2017). Epigenetic mechanisms of alcoholism and stress-related disorders. Alcohol, 60, 7–18. https://doi.org/10.1016/j.alcohol.2017.01.001
[28] Barsha Mohini Das, "IMPACT OF COVID PANDEMIC ON THE LIFE OF ARTISTS", Global Research Journal-3, London Organisation Skill Development Ltd, Vol. 1, issue 3, pp. 16-21. https://globalresearchjournal.info/https-globalresearchjournal-info-publications/
[29] Dr Michelle Nemec, "REBOOT, REBOUND AND RECOIL - THE ROLE OF RESILIENCE FOR INDIVIDUALS AND ORGANISTIONS IN THE COVID-19 PANDEMIC", Global Research Journal-3, London Organisation Skill Development Ltd, Vol. 1, issue 3, pp. 22-27. https://globalresearchjournal.info/https-globalresearchjournal-info-publications/
[30] Prof. Baliram N. Gaikwad, "Education During Covid- 19 Pandemic and the Compounding Challenges in India", Global Research Journal-3, London Organisation Skill Development Ltd, Vol. 1, issue 3, pp. 28-30. https://globalresearchjournal.info/https-globalresearchjournal-info-publications/
[31] Aditi B. Gaikwad, "COMPREHENDING THE LINGUISTIC AND PSYCHOLOGICAL IMPACT OF COVID-19", Global Research Journal-3, London Organisation Skill Development Ltd, Vol. 1, issue 3, pp. 31-33. https://globalresearchjournal.info/https-globalresearchjournal-info-publications/
[32] Dr. Monica Sharma, "EFFECTS OF THE COVID-19 PANDEMIC ON INNER PEACE AND HAPPINESS", Global Research Journal-3, London Organisation Skill Development Ltd, Vol. 1, issue 3, pp. 34-38. https://globalresearchjournal.info/https-globalresearchjournal-info-publications/