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The Role of DNMT Inhibitors in Type-2 Diabetic Retinopathy

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Abstract: ***Type II diabetic retinopathy is one of the familiar problems of diabetes which is considered by differences in retinal blood vessels. Epigenetic modifications participates vital role in various diseases such as diabetic retinopathy is nowadays a rising area. Numerous possibilities for treatment of diabetic retinopathy through epigenetic modification have been studied in various review articles. With the increasing proof of epigenetic modifications in case of diabetic retinopathy, better consideration of these modifications has latent to recognize novel targets to prevent this disease. The Dnmt inhibitors (DNA methyltransferase), 5-aza-20-deoxycytidine and 5-azacytidine together have been agreed by the FDA. More distant studies have observed that the reaction of those compounds on diabetic retinopathy where in they appear to slow down the process of methylation with few favourable outcome at decreasing the symptoms. Some demethylating agents may be favourable in the treatment of diabetic retinopathy. So, the effects of demethylating agents can be used to check the expression levels of BDNF gene and if they give better results then it may use as personalized medicine in future to block or slow down the progression of type II diabetic retinopathy.***

Keywords: Epigenetics, genetics, diabetic retinopathy, BDNF, demethylating inhibitors.

I. INTRODUCTION

In the 21st century, diabetes is one of the most consequential health problems (Gouri and dekaken, 2013). It is a condition where blood glucose levels turn into too high as the body either produces little or no insulin. In India, it is quick growing rank of a probable epidemic with more than 62 million diabetic persons presently diagnosed with the disease (Kaveeshwar and Cornwall, 2014). In 2000, India-31.7 million topped the world with the maximum number, China-20.8 in second and United States -17.7 in third rank in the case of diabetes population (Kumar et al., 2013; Joshi and Parikh 2007). According to reviewed literature, the popularity of diabetes is estimate double worldwide from 171 million to 366 million in 2000 to 2030 with an utmost increase in India. In 2030, it is expected that diabetes mellitus may bother up to 79.4 million persons in India, in China - 42.3 million and in US -30.3 million will also notice major raise in those affected by the disease (Shaw et al., 2010; Whiting et al., 2011).

Especially in the most developed countries diabetic retinopathy is one of the most significant causes of blindness globally (Resnikoff et al., 2004; Bourne et al., 2012). Type II diabetics have diabetic retinopathy lesions up to 20% at the time of diagnosis, and >60% of the patients have developed diabetic retinopathy after 20 years of evolution of the illness. According to different studies the proportion of diabetic patients who have never undergone an ophthalmoscopic examination exceeds 30% (Vidal-Alaball et al., 2019). Diabetic retinopathy is considered by the development of fresh blood vessels which is characterized into proliferative diabetic retinopathy and non-proliferative diabetic retinopathy. The development of DMO (diabetic macular-oedema) may or may not engross by non-proliferative diabetic retinopathy which is further separated into mild, moderate, and harsh stages. The most important causes of harsh visual impairment are proliferative diabetic retinopathy and diabetic macular oedema. In the case of type II diabetes, approximately all patients with type I diabetes are, by the first decade of incidence of diabetes expected to have some form of retinopathy (Tarr et al., 2013).

Diabetes, hyperglycaemia and hypertension are the most clinically vital danger issues for progression to vision loss. For preventing vision loss due to diabetic retinopathy is to control glucose in serum and blood pressure have been shown to be effectual (Lee et al., 2015). In retina, chronic hyperglycaemia results in oxidative stress and capillary injury and in try to recompense for the loss, an events cascade is begin to form new blood vessels. Therefore fragile and leaky vessels are formed and it cause edema in the retina effecting in visual impairment helped by other traits such as blood retinal barrier breakdown, basement membrane thickening, pericytes loss, etc (Shubhra et al., 2018; Viswanath 2003).

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II. GENETICS AND DIABETIC RETINOPATHY

For any sort of disease, pathogenesis is affected by genetic factors. Therefore, genetic factor has crucial role in the prediction of diabetic retinopathy between the diabetic patients with similar risk factors. But, such genetic organizations are not yet clearly founded. Various of genetic variants have been identified by landmark "Genome-Wide Association Studies" that could describe some of the inter individual variations in the vulnerability of diabetes (Torres et al., 2013). A meta- analysis study, it is a kind of study which used to look into feasible genetic alliances with type II diabetic retinopathy, which integrated reports published between January 1990 and August 2008, it has represented a major variation in the AKR1B1 (aldoketoreductase family 1 member B1) gene. This gene encodes AKR1B1 (aldoketoreductase family-1, member-B1) and in polyol pathway, it act as rate limiting enzyme. Polyol pathway is also pathways that involved in the progression of diabetic retinopathy (Frank 2004; Kitada et al., 2010). According to reviewed article has explained that receptor-ɣ2 gene turn on by the Ala allele of the polymorphism of Pro12Ala in the peroxisome proliferators activated receptors. Peroxisome proliferators activated receptor-ɣ2 gene acts as a protective gene in the incidence of retinopathy in type II diabetic patients (Jinlan et al., 2012). Current studies haven't succeeded to discover any relations between vascular endothelial growth factor **(**VEGF)-related single nucleotide polymorphisms (SNPs) (rs6921438 and rs10738760) and the risk of nephropathy and diabetic retinopathy in diabetic patients (Bonnefond et al., 2013). As a result, the connection between diabetic retinopathy and genetic factors remains to be elucidated. Duration of the disease, the probability of diabetic retinopathy is increase and type II diabetes has a risky beginning and it can go unnoticed for years. Therefore, during diagnosis, already patients may own type II diabetic retinopathy. However, type II diabetics don't typically develop retinopathy until years after the diagnosis is made and they are diagnosed early in the course of their disease. After puberty, the risk of growing retinopathy is increases. Twenty years after the diagnosis of diabetes, nearly all type I diabetics and 80% of type II diabetics be evidence for some indications of retinopathy (Shubhra et al., 2018).

III. EPIGENETICS AND DIABETIC RETINOPATHY

Epigenetic which is also recognized as "external genetics," "post-genetics," or "prefix genetics," representing, do not involve of changes in sequence of DNA in which the function of genes could go through transformation that are heritable and reversible. Sometimes, it also called to the studies on the procedure of physiological development (Moosavi and Ali 2016). Epigenetic modification includes acetylation of histone, non-coding RNA regulation and DNA methylation. These epigenetic modification are basically engaged in the growth of a variety of diseases along with autoimmune diseases, cancer, psychiatric diseases, addictive diseases and neurodegenerative diseases (Portela and Esteller 2010). Optic nerve diseases such as keratitis, dry eye, glaucoma, uveitis, fundus neovascularisation and myopia may also be related with epigenetic modifications. Current studies revealed that, DR (diabetic retinopathy) is an imperative reason of blindness amongst the working inhabitants; it has attracted particular concentration because of its high rate of causing blindness, increasing incidence, and consequence in health of public. Epigenetic modification for example methylation of DNA, histone modification, microRNA (non-coding RNA) is talk about below,

A. DNA methylation

In epigenetic modification, DNA methylation is the first discovered process. In these mechanism, a methyl group is add on position 5 of C (cytosine) residues of the cluster of CpG island (CpG dinucleotides), CpG island is the regulatory region of the majority genes which is typically linked with transcriptional repression (Deaton and Bird 2011; Williams et al., 2011). CpG exists mostly in two types: one grouped is known as the CpG islands and other evenly distributed throughout the sequences of DNA which 60–90% are methylated in mammalian cells. They are commonly originate in the regulatory regions of coding genes and CpG islands are participated in chromatin structure modification and expression of gene in the eukaryotic cells (Portela and Esteller 2010). According to reviewed article, there are five enzymes which have been identified as part of family of DNA methyltransferase (DNMT), such as DNA methyltransferase1 (DNMT1), DNA methyltransferase2 (DNMT2), DNA methyltransferase3a (DNMT3a), DNA methyltransferase3b (DNMT3b), and DNA methyltransferase3L (DNMT3L); to active DNA methylation only DNA methyltransferase1 (DNMT1), DNA methyltransferase3a (DNMT3a), and DNA methyltransferase3b (DNMT3b) are use. DNA methylation is also affecting the protein-DNA interaction by deactivates the target genes or causes conformational changes in DNA. There are three conditions of DNA methylation in human body such as persistent hypomethylation, induced demethylation, and hypermethylation. Methylation are nearly associated to progression of disease; hypermethylation and persistent hypomethylation are originate in some type of cancer cells (Zhang et al., 2017).

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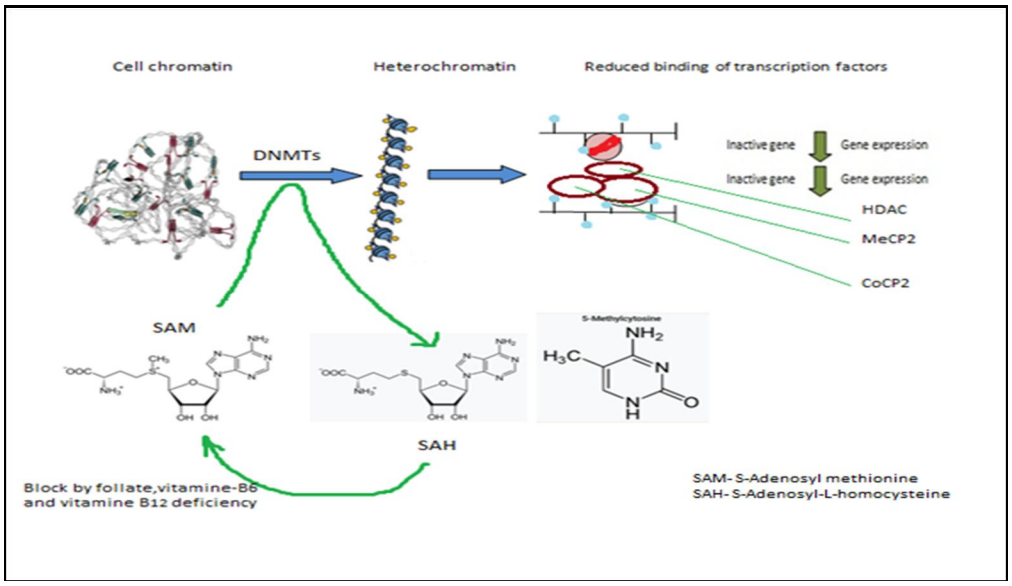

Figure 1**:** DNA methylation - DNA methylation is arbitrated by DNMT (DNA methyltransferase) enzymes at sites of CpG. DNA methylation can also diminish expression of gene by raising the binding of MECP (methyl-CpG-binding proteins) or decreasing the binding of transcription factors (Moosavi and Ali 2016).

B. Histone Modification

Histone modifications, it refers to phosphorylation, acetylation, methylation, ADP-ribosylation adenylation, ubiquitination, and other histones modifications in the existence of associated enzymes. In epigenetic, histones are an essential element and the core histones such as histone 2A (H2A), histone 2B (H2B), histone 3 (H3), and histone 4 (H4), it could form a nucleosome with one histone 3 (H3)– histone 4 (H4) tetramer and two histone 2A (H2A)– histone 2B (H2B) dimmers (Portela and Esteller 2010). The shape of histone core is spherical and the N-terminal protein tails does not make up the nucleosome because they are unorganized hisH1 which is the linker histone. It rather binds to the linker DNA after that it repaired the location of the nucleosome for the entry and outlet of DNA (Daujat et al., 2005). Histone modification which is playing a important role in controlling the transcription of DNA, replication and repairing as well as differential splicing and condensation of chromosome (Zhang et al., 2017).

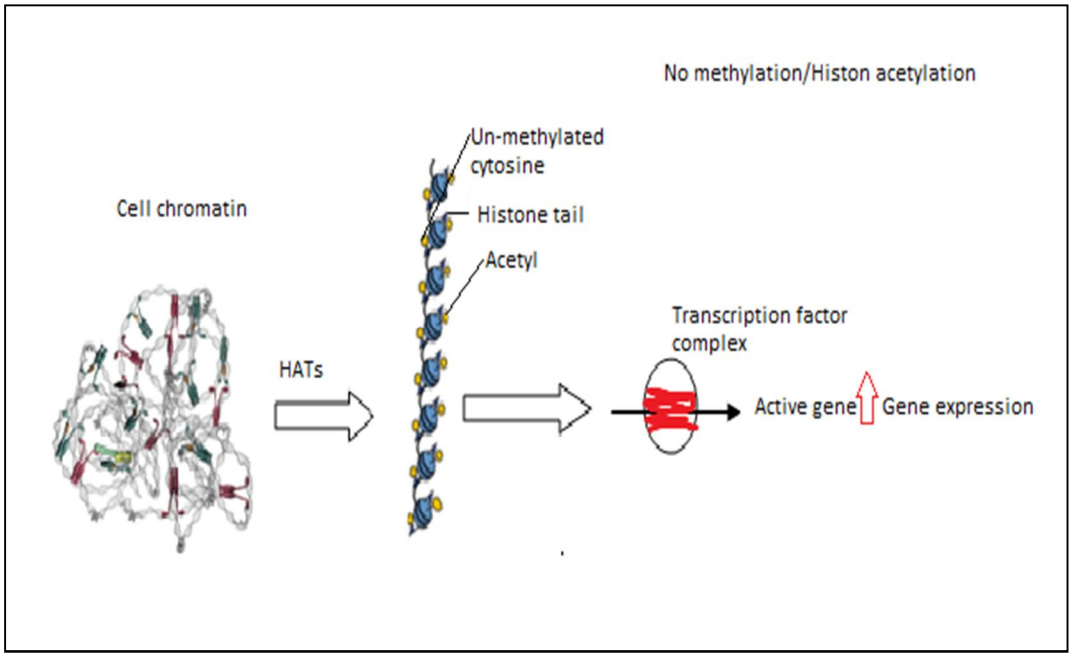

Figure 2: Histone modification- It is vital histone modification that can speed up transcription factors binding and then expression of gene next to DNA demethylation (Moosavi and Ali 2016).

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C. Non-coding RNA

Non-coding RNA, they don't code proteins and it consist of those with familiar functions such as tRNA, rRNA, snRNA, microRNA (miRNA), snoRNA, circular RNA and others with unfamiliar functions. MicroRNA is engaged in post-transcriptional regulation and it is a single strand RNA that having 21–25 nucleotides. By suppressing the protein translation microRNA or degrading the RNA which can bind to the target sequences of 3′-UTR and regulate the activity of mRNA (He et al., 2004). It controls the expression of less than 60% proteins in the case of mammals and this procedure also influence 1/3rd of the whole genome in human. Also, microRNA takes parts in different pathological procedure such as the inhibition of translation, the inhibition of translation initiation along with the regulation of mRNA degradation and deadenylation. Individual microRNA has many target genes and the same gene which can be control by dissimilar microRNAs because protein translation inhibition is a critical regulation pathway and the composite method of non-coding RNA understands the well control of expression of gene (Bartel 2013).

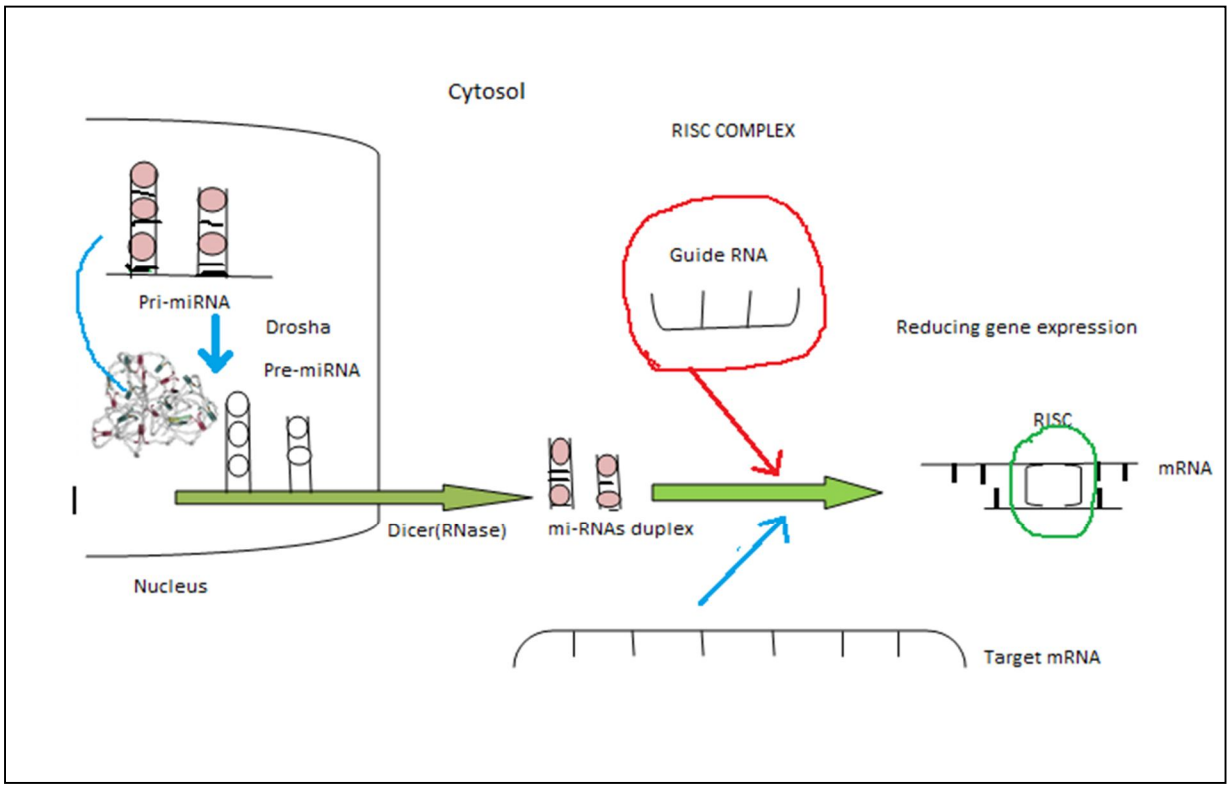

Figure 3: Involvement of microRNA in epigenetic modification- microRNA formation starts in nucleus and it go on in cytosol which can carry out a method to control expression of gene in mRNA level (Moosavi and Ali 2016).

IV. RETINOPATHY AND CANDIDATE GENES

A. Vascular endothelial growth factor gene (Human chromosome 6p12)

During the appearance of macular edema in diabetes patients, VEGF plays a vital role in the neovascularisation in proliferative diabetic retinopathy and also in the crumble of blood-retinal barrier (Liew et al., 2010), in turn altering retinal capillaries permeability by improving protein phosphorylation content indulged in the stretched-junctions similar to zonula occludens (Antonetti et al., 1999). Considerably, raised vitreous levels of VEGF molecules had been a main hindrance reported in case of diabetic retinopathy patients (Liew et al. 2010; Sydorova and Seng 2005). Mitogen-activated proteins activate by induction of VEGF molecules which causes endothelial cell proliferation. VEGF molecule is inducing which turn on mitogen-activated proteins that causing the proliferation of endothelial cell and this signalling cascade overlies with arousal of phophatidylinositol 3-kinase pathway after VEGFR-2 is induce (Ferrara 2004). Vascular endothelial growth factor– A (VEGF-A) , it starts the endothelial cells to release matrix metallo-proteinases and the degradation of membranes exactly basement membranes by urokinase-plasminogen activator which help in cell migration (Hoeben et al., 2004). For capillaries formation when the basement membrane is developed then, passage and propagation of vascular endothelial cells are tailed and for the solidity of freshly formed capillaries is achieved by assisting pericytes and soft cells of muscle that are managed by PDGF (platelet derived growth factors) (Jennifer et al., 2004).

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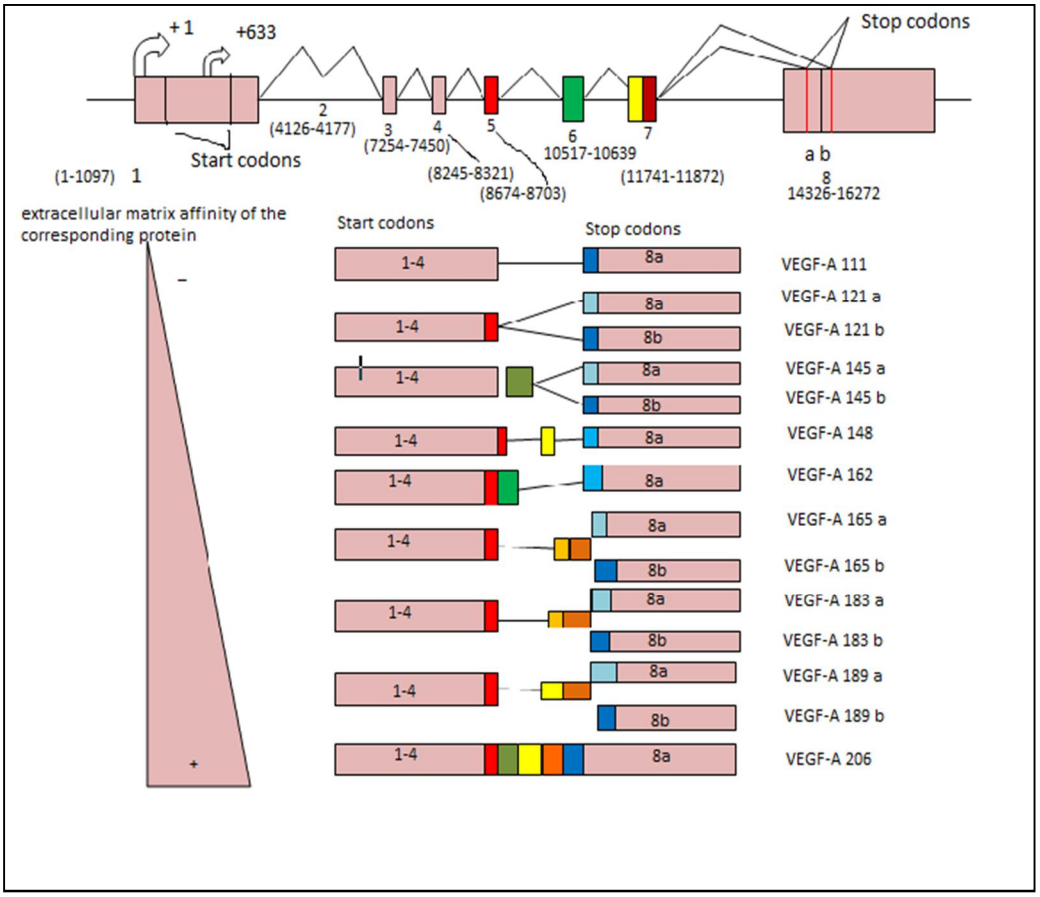

Figure 4**:** Structure of vascular endothelial growth factor..

Human vascular endothelial growth factor gene A (VEGFA) gene structure and exon composition of the isoforms created by alternative splicing and human vascular endothelial growth factor gene A **(**VEGFA) gene spans 16272 base pair of chromosome 6p12 and it consists of 7 introns and 8 exons. The two main starting sites of transcription, the two starting sites of translation (CUG and AUG) in the 1st exon and 2 substitute stop codons in exon 8 are designated. All presently explained isoforms have exons 1–5 and two different exons 8. The choice of the terminal exon splice site results in two isoform families such as the anti-angiogenic vascular endothelial growth factor gene –Axxxb (VEGF-Axxxb) and the pro-angiogenic vascular endothelial growth factor gene –Axxx (VEGF-Axxx) family. Exons six and exon seven determine heparin-binding domains which is accountable for the diffusibility and extra cellular matrix affinity of the alternative spliced isoforms (Lacazette et al., 2013).

B. Aldose Reductase gene (ALR/ALR2/ AKR1B1, Human Chromosome 7q35)

In polyol pathway, ALR is the foremost enzyme. It is oxidoreductase (monomer), via nicotinamide adenine dinucleotides phosphate hydrogen (NADPH)-dependent reduction, the catalysis of various carbonyl compounds is carrying out, containing its major target glucose. Aldose reductase has a single domain, a crystal structure, parallel α/β-barrel motifs (folded) and 8-stranded comparable which containing the binding site of substrate position at the carboxy-terminal of the β-barrel (Brownlee 2001). The gene which is encoding for aldose reductase is situated on 7q35 chromosome (Kovacs et al., 2006; Abhary et al., 2009) and it participates rerun polymorphism A-C at 5′end. This repeat polymorphism is related in the relevant studies with diabetic retinopathy in population of India (Upadyay et al., 2003), Chileans (Olmos et al., 2000), population of China (Wang et al., 2003), population of Brazil (Richeti et al., 2007), population of Hong Kong (Ko et al., 1995; Lee et al., 2001) and in population of Japan (Fujisawa et al., 1999). Aldose reductase has a shortened affinity for glucose molecules in non-diabetics patients that controlling the metabolism of these molecules in a minute proportion of the overall glucose exploited. Alternatively, a patient who have hyperglycemias, when intra-cellular glucose is increased then resulting in increased enzymatic conversion to the poly-alcohol sorbitol, with a immediate decrease in the level of NADPH (Obrosova and Kador 2011; Brownlee 2001).

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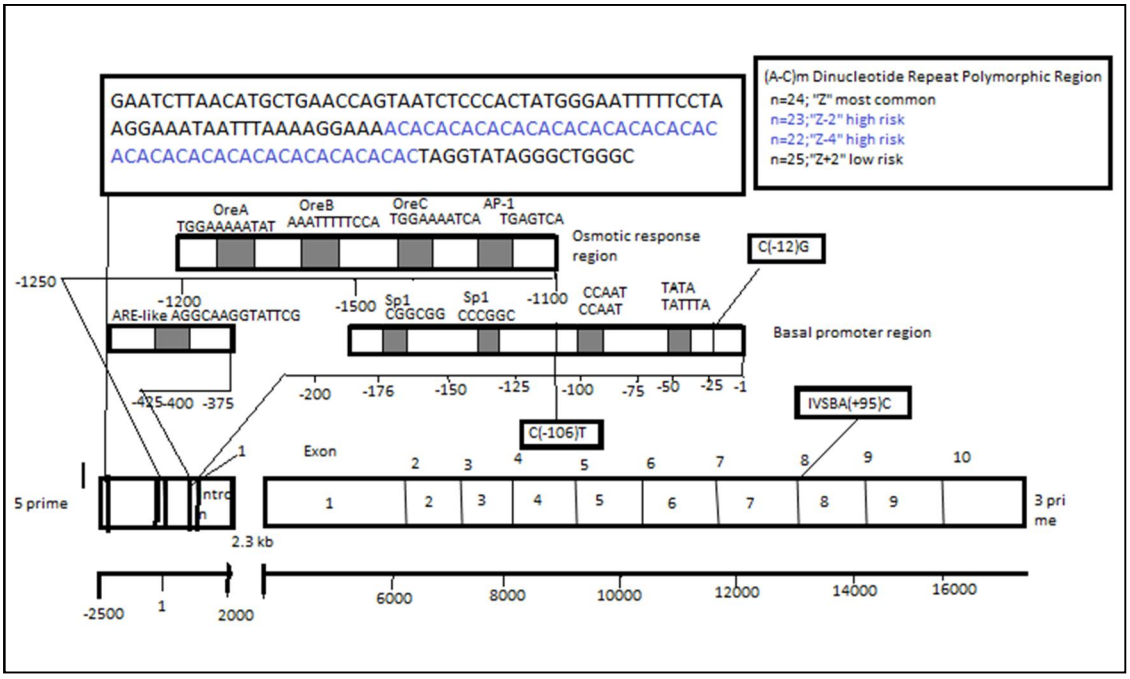

Figure 5: Structure of the human aldose reductase (AKR1B1) gene (Lorenzi 2008).

C. Brain Derived Neurotrophic Factor (BDNF, Human Chromosome 11p14.1)

BDNF, it is a part of the neurotrophic factor family. For aggregation of Aβ and tau proteins, BDNF is well-known to keep safe against neurotoxicity of the Aβ peptide and death of neural cell (Aicardi et al., 2004). It is crucial in modifying memory-associated neuroplasticity through proliferation, synaptic growth and controlling cell survival in the progressing central nervous system (Poo 2001; Egan et al., 2003). BDNF which can encourage long-term potentiating, it is believed to be the neuro-physiological source for memory and learning (Costenla 2011). Also, BDNF hindrance signalling by antisense RNA and gene knockout that harm spatial memory and learning (Guzowski et al., 2000). Many current studies have confirmed that serum levels of BDNF are considerably lesser in patients with cognitive diseases, for example Alzheimer's disease (Gunstad et al., 2008), Huntington's disease (Ciammola et al., 2007) and mild cognitive impairment.

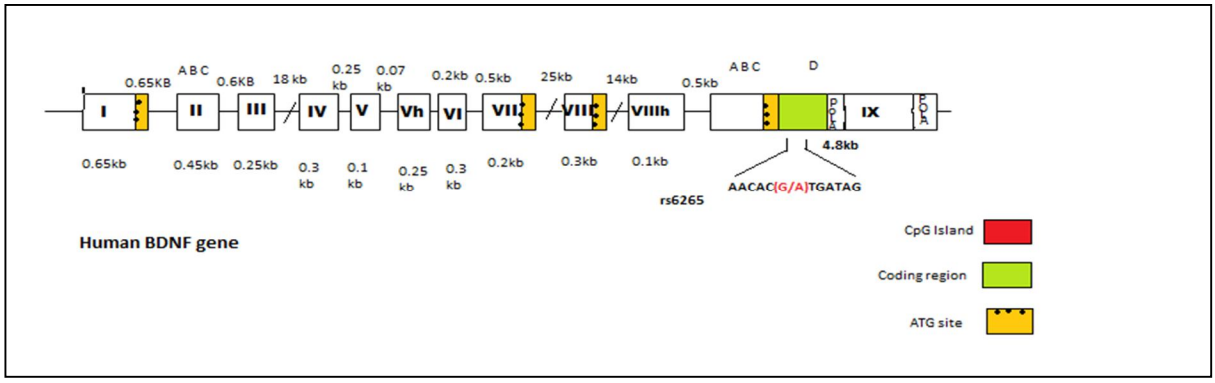

Figure 6: Structure of the human brain-derived neurotrophic factor gene.

Introns are represented as lines and exons are symbolized as boxes. The size of introns and exons is specifying in Arabic numbers and numbers of the exons are designated in roman numbers. The 30 coding exons (exon IX) having 2 polyadenylation sites (poly A). The start codon ATG is symbolized by red boxes that mark transcription initiation. The green boxes represent the region of exon IX coding for the pro-brain-derived neurotrophic factor protein, as well as the rs6265 genetic variant involved in the polymorphism of Val66Met. There are some exons, like exon II and IX which have dissimilar transcript variants with alternative splice-donor sites (A, B, C and D). With the help of Meth primer, CpG islands were predicted and concluded as sequences of at least 200 bp with a GC % greater than 50% (Boulle et al., 2011).

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V. RELATIONSHIP BETWEEN BRAIN-DERIVED NEUROTROPHIC FACTOR AND TYPE-2 DIABETIC RETINOPATHY

BDNF is related with systemic inflammatory conditions, for example diabetes (Krabbe and Nielsen 2007). Current studies revealed that BDNF which may provide to metabolism of glucose and it has a pathogenic function in the progression of T2DM. Comparison between normal patients and T2DM patients, levels of BDNF serum were drastically lesser in advanced T2DM patients than normal patients (Fujinami et al. 2008). For diagnosis of type II diabetes mellitus, serum levels of BDNF as an indicator, depend on the receiver operating characteristic curve. BDNF, it can be identify as an indicator and the study of independent diabetes complications recommended that little levels of BDNF lead decrease glucose metabolism. Most decisively, studies has been exposed that reduced BDNF were related with diabetes complications and obesity (Ola and Imtiaz 2013). Plentiful studies revealed that BDNF serum levels in diabetic animals and in diabetic patients, which show a relationship with reduced glucose, lipid metabolism and insulin resistance, serum levels of BDNF were oppositely associated with fasting glucose. In other words, decreased BDNF serum levels in the retina of diabetic rats and in diabetic retinopathy patients (Ola and Imtiaz 2013).

BDNF is essential for development and the differentiation. Previous studies was established that at early stage of diabetic retinopathy, particular retinal ganglion cells experience retinal neurodegeneration and apoptosis and it is likely to be associated with a shortage of BDNF (Fernyhough et al., 2003). BDNF is critical for photoreceptor cells such as rods and cones and the repair of damage to the retina and the optic nerve. BDNF, it is exhibited in ganglion cells of retina and in the retinal muller glial cells (Seki et al., 2003). BDNF encourages survival in damaged retinal ganglion cells (Johnson and Thoenen 1986) and it also encourages the nerve fibre regeneration (Mey and Thanos 1993; Mercedes et al., 1996). Furthermore, BDNF encourages retinal inter-neurons survival and it is also significant for initiating synaptic and phenotypes relationships in the growing retina (Arango et al., 2004). BDNF, it has been revealed to prevent cell death of neuro-retinal cells under situations of cardiac ischemia and to prevent apoptosis in retinal ganglion cells of rat at early stages of diabetic retinopathy. On the other hand, the methods by which BDNF either controls retinal ganglion cells or not remain unsure (Mu et al., 2007; Murphy et al., 2007; Liu et al., 2007). TrkB is a receptor of BDNF protein which engaged in the maturation and progression of the peripheral and central nervous systems. According to reviewed article have revealed in vivo that retinal neurons death at initial stages of type II diabetic retinopathy associates with reduced BDNF levels, TrkB receptor which is necessary for the protection of neurons of brain and retinal ganglion cells persuade by BDNF. But, it is not sure whether BDNF defends neurons of retina exposed to hyperglycemia in vitro or not and it is not clear whether the ERK/MAPK pathway is turn on in response to BDNF persuaded protection of neuron. When the cells represent to hyperglycemia condition, it showed signs of excessive levels of apoptosis, whereas BDNF prevent apoptosis mediated by hyperglycemia. Inside the cells, BDNF have defensive effects which was a positive connection between BDNF and the survival of diabetic eye neuron (Yadav et al., 2018).

VI. DNA METHYLATION INHIBITORS AND DISEASES

In cancer and other diseases like diabetic retinopathy, gene silencing by abnormal methylation of promoter regions of genes are difficult for usual cellular functions (Jones et al., 2002). Critical genes has been epigenetically inactivated which can be determined by broad variety of tumour types, containing DNA repair genes, tumour suppressor genes, apoptotic genes, cell-cycle regulatory genes and genes involved in metastasis, invasion and angiogenesis (Costello and Plass 2001). When these genes are reactivated in the cancer cells, resulting in cell growth suppression and differentiation or raised sensitivities to existing therapies (Plumb et al., 2000). Epigenetic modification, they are likely reversible, which makes them prepossessing goals for therapeutic intervention. Whilst hypomethylation following treatment by DNA methylating inhibitors is suggest to cause chromosomal instability and it seems more applicable to embryonic tissues (Li et al., 1992; Okano et al., 1999) than to adult tissues (Laird et al., 1995). For that reason, using of demethylating agents could reactivate key genes and remodelling normal function of cells seems like a reasonable way to move towards the problems of cancer treatment and other diseases like diabetic retinopathy. Numerous possibilities for treatment of DR (diabetic retinopathy) through epigenetic modification have been investigated; one proposal is to prevent the methylation of MMP-9 and SOD2. The DNA methyltransferase inhibitors, 5-aza-20-deoxycytidine and 5-azacytidine both have been agreed by the food and drug administration (FDA) for the treatment of some diseases. More distant studies have observed that the reaction of those compounds on diabetic retinopathy where in they seem to slow down the methylation process with few success at decreasing the symptoms. According to current studies showed that there has been mounting attention in the progression of epigenetic therapy which engaging the use of histone deacetylase inhibitors and DNA methylation inhibitors (Egger et al., 2004).

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VII. CONCLUSION

In the case of type II diabetic retinopathy, epigenetic mechanisms are hypothesized to participate a vital role because they provide a method for continued modify expression of gene. Previous studies have been reported that site-specific DNA methylation is induced by hyperglycemia and the expression levels of DNA methylation of BDNF gene between the diabetic patients and normal person can be significant in the initiation of cause of type II diabetic retinopathy and clues about their exclusive role in disease pathogenesis. Recent evidence suggested that some demethylating agents may be useful in the treatment of diabetic retinopathy. So, the effects of demethylating agents can be used to check the expression levels of BDNF gene (i.e. increase BDNF expression or decrease BDNF expression) and if they give better results then it may use as personalized medicine in future to avoid or slow down the development of type II diabetic retinopathy.

VIII. ACKNOWLEDGEMENT

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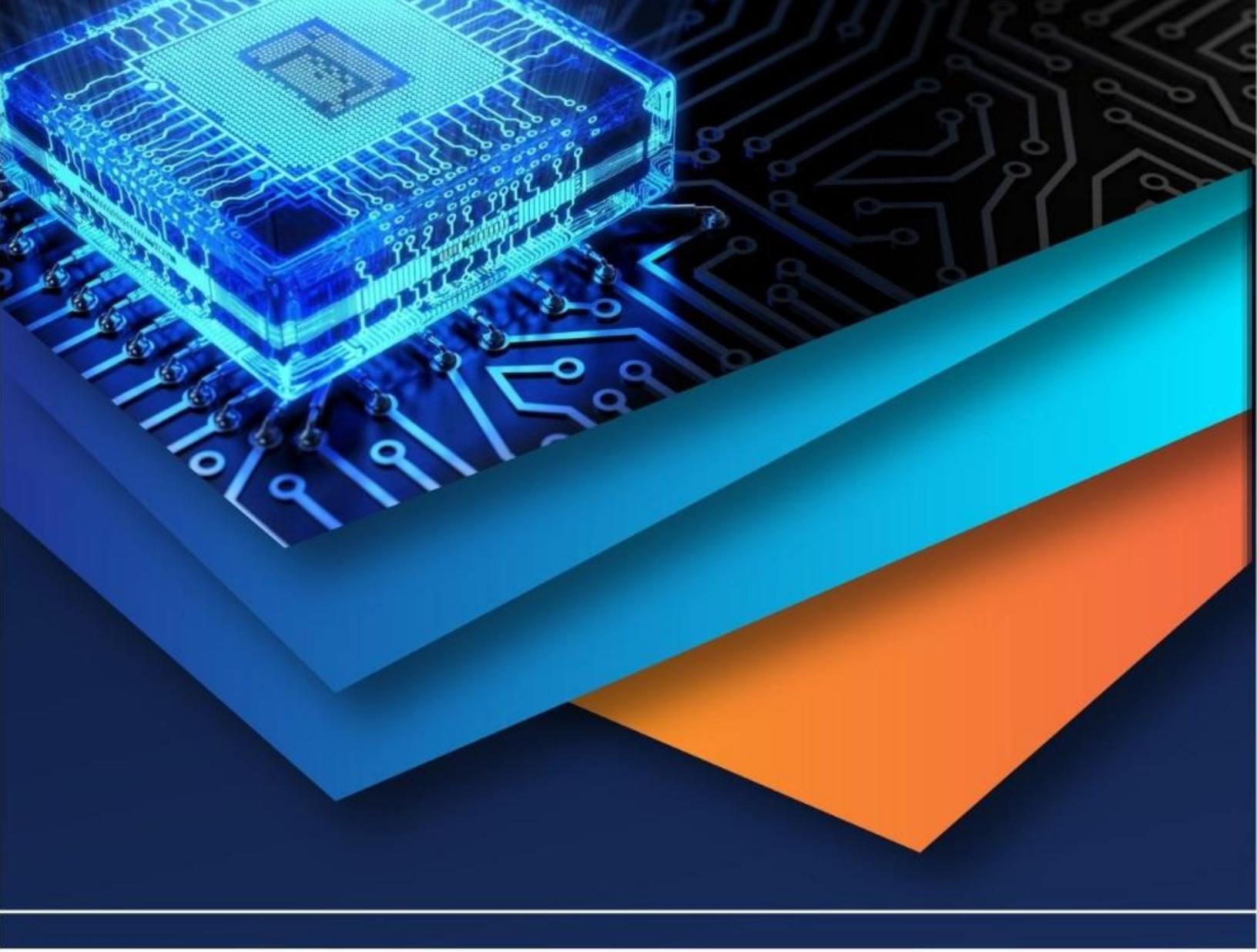

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