INTELLECTUAL DISABILITY CLASSIFICATION, CAUSES, EPIGENETIC MECHANISMS AND TREATMENT

ANJUM R¹, REHMAN AU², MAQSOOD H³, ILYAS U³, NIAZ M³, ROHAIL⁴, MOHSIN S⁵*, JURRAT H⁴, ANJUM S⁵, MUNAWAR I⁶, HAMID M⁶, ZAFAR MZ²*

¹Department of Zoology, Government College University, Lahore, Pakistan
²Faisalabad Medical University, Allied Hospital Faisalabad, Pakistan
³Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
⁴Department of Zoology, Riphah International University, Faisalabad Campus, Pakistan
⁵Shaukat Khanum Memorial Cancer Hospital & Research Centre, Pakistan
⁶Registrar, Family Physician, King Saud University Medical City, Riyadh, Saudi Arabia
*Correspondence author email address: sehrishmohsin@gmail.com; mashod@live.com; zafarzubairrana@gmail.com

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Abstract: Intellectual disability (ID) is a condition characterized by a defective adaptive and cognitive attitudes that can occur with various mental disorders, such as attention-deficit/hyperactivity and an autism spectrum disorder. It may also be associated with malformation syndromes affecting other organs. Genetic studies have linked several chromatin-modifying enzymes and epigenetic regulators to ID disorders (IDDs). This review explores how dysfunction in histone modifiers, chromatin remodelers, and methyl-DNA binding proteins can cause neurodevelopmental deformities and alter brain plasticity. The use of mouse models generated through human genetics has allowed researchers to uncover the molecular basis of ID and explore potential therapeutic strategies. Understanding the chromatin regulators associated with IDDs has broader implications for treating other IDDs, as they target common downstream genes and cellular functions. Investigating these disorders can also shed light on the function of chromatin regulators in brain growth, plasticity, and gene regulation, leading to new insights into fundamental questions in neurobiology.

Keywords: Intellectual disability, Epigenetic, Malformation syndrome

Introduction

Intellectual disability (ID) can result in incomplete or arrested mental development. It is characterized by the deterioration of cognitive, language, motor, and socialization functions at each stage of development, leading to an overall low level of intelligence. Individuals with ID struggle to adapt to their environment due to the pervasive impact of their cognitive impairments. Generally, a person with an intelligence quotient (IQ) of 70 or below has two or more behavioural deficits. The IQ is the standard test developed to assess the disability in humans (Selmén et al., 2005). In ID, the patient finds difficulty in daily activities such as communication, personal care, sociability, self-governance, health and safety, and academic skills (Matson et al., 2005). It is mostly diagnosed before the age of 18 years when a person is unable to perform properly or is diagnosed with adaptive functioning (Gorgoni et al., 2020). The ID Occurrence rate is 1 to 3% of the total population and independent of social stratum (Maulik et al., 2011).

Instead of the universal data, it is shown that ID is more common in the lower socioeconomic status and developing areas, where its severity occurs from mild to worse depending on the treatment (Durkin, 2002; Emerson, 2007). ID is likely to occur because of Ecological factors (Luckasson, & Schalock, 2013; Emerson, 2002), but genetic factors contribute equally. In the general population, about 30% more males are affected by ID than females. But it is believed that as IQ decreases, the prevalence of ID aldecresaseed (American Psychiatric Association, 2002). Previous research showed that severe ID is more prevalent in females than males (Bradley et al., 2002).

Classification of ID

ID is classified into four general categories that is mild, moderate, severe and profound (Matson et al., 2005). But some epidemiological studies classified ID into two categories: mild ID with IQ 50-70 and severe ID with IQ<50 (Ropers and Hamel, 2005).
occurrence of ID differs depending upon the study design, and the age of the subject caused the variabilities (Leonard and Wen, 2002), as shown in Table 1.

ID's severity can be divided into syndromic intellectual disability (SID) and non-syndromic intellectual disability (NSID). In the SID, the patient usually has one more clinical feature: co-morbidities besides ID. While the NSID, the patient has ID as the only clinical feature. But to create the boundary between SID and NSID is difficult. Diagnosing one or more clinical features (neurological and psychiatric abnormalities) in these patients is very difficult to rule out. Also, the ID syndromes are so subtle that they are very difficult to find as they may be linked to genetic defects (Ropers, 2006).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classification of intellectual disability from mild to profound.</th>
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<tbody>
<tr>
<td>Level</td>
<td>IQ Range</td>
</tr>
<tr>
<td>Mild</td>
<td>50-69</td>
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<tr>
<td>Moderate</td>
<td>35-49</td>
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<tr>
<td>Severe</td>
<td>20-34</td>
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<tr>
<td>Profound</td>
<td>Below 20</td>
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Causes of ID
The environmental, genetic factors or both contribute to ID. There are about 60% unknown cases of ID which remain unidentified (Rauch et al., 2006). The environmental causes of ID include exposure to toxins, teratogens, viruses or radiation, which can damage (severe head trauma or injury) brain cells and cause a lack of oxygen in the brain tissues, which eventually die and causes more damage to brain. These factors mostly occurred due to the lack of awareness in underdeveloped or developing countries.

![Figure 1](image_url) Causes of intellectual disability (ID) with examples. ID is caused by genetic and non-genetic factors. In the genetic factors, X-fragile syndrome, X-fragile syndrome, and Down's syndrome are more common. On the other hand, the non-genetic factors are the environmental such as malnutrition or acquired in any stage of pregnancy or the head trauma even in the adult life causes the ID. Many other factors contribute to ID which are still unknown.

**Genetic factors**

Genetic defects cause the majority of cases of intellectual disability (ID). Specifically, about 25-50% of cases of ID are attributed to genetic defects, and this proportion tends to increase with the intensity of the ID (McLaren and Bryson, 1987). The most common cause of ID is chromosomal abnormalities, and numerous abnormalities are found (Rauch et al., 2006). Autosomal trisomies and X-chromosome aneuploidies are often associated with intellectual disability (ID) in humans due to their link to genetic instability. Down syndrome, caused by trisomy 21, is a frequent form of ID. Numerous genetic components have been recognized that participate in the development of ID (Zahir and Friedman, 2007). The less common forms of chromosomal abnormalities include X-fragile chromosome syndrome (Miclea et al., 2015), Prader-Willi syndrome (Jauregi et al., 2007), Rett syndrome (Weaving et al., 2005), neurofibromatosis (Mouridsen and Sorensen, 1995), tuberous sclerosis (Curatolo et al., 2015), Lesch-Nyhan syndrome (Nyhan et al., 1989) and adrenoleukodystrophy (Feanny et al., 1987) rarely occur (Figure 1). In the last 15 years, many forms of NSID were identified due to environmental and genetic factors. Autism or neurodevelopment disorder is likely to be occurred by genetic basics, or environmental factors may contribute equally. The NSID is multifactorial, with one or more genes involved in the disease. It can either be autosomal or X-linked (Chelly et al., 2006).

**Acquired factors**

Acquired factors may be congenital or developmental. The congenital factors include the neonatal metabolic hypothyroidism, toxins such as lead poisoning (Tellez-Rojo et al., 2006), fetal alcohol syndrome (Kodituwakku, 2007) and prenatal exposure to substances (Morrow et al., 2006), and the infectious diseases such as rubella (Desmond et al., 1969), syphilis (Gilad et al., 2007), toxoplasmosis (Tomita et al., 2021) and simple herps genital type II (Seppanen et al., 2006).

During pregnancy, in the prenatal period, complexities such as uncontrolled diabetes (Leonard et al., 2006), intrauterine malnutrition (Calis et al., 2007), vaginal hemorrhages (Schellae et al., 1994), placenta previa (Naeye, 1978) and umbilical cord prolapse (Niswander et al., 1975). Also, in this period, prolonged suffering from anoxia and asphyxia related suffocation also retard the growth of brain tissues (Slitenon et al., 2003). In postnatal period, infectious diseases like encephalitis and meningitis affects the fetus (Noyola et al., 2001) shown in figure 2.

**Environmental and socioeconomic factors**

Many epidemiological studies showed that intellectual disability mostly related to family status. There are many notable links between ID and poverty. Firstly, poverty exposes the person to many environmental and psychotic stimulus (Leonard et al., 2005). Second, if a person in the poor family has ID, it more causes a burden on the other family members. These factors are mostly affected in the developing countries (Emerson and Hatton, 2007). These interactions result in the child's malnutrition in prenatal, postnatal and even at the younger age.

**Epigenetic mechanisms in ID**

The ID is mostly affected by epigenesis, which is the not the change in the DNA sequence but only regulated the chromatin state in the DNA (Waddington, 1956). These mechanisms are interrelated, but chromatin compaction is the only thing common in them. Impaired transcription results in the loose of the facilitated gene. The molecular mechanisms still need to be explained. Epigenetic mechanisms participate in coordination among genes and the environment, particularly in learning and memory processes. These mechanisms contribute to brain plasticity, which involves modifying neuronal structures in response to external inputs. Recent studies have demonstrated that neural impulses initiate the production of new proteins in dendrites, which in turn affect the function of postsynaptic neurons (Cajigas et al., 2010). This review highlights the epigenetic dysregulation in ID.

1. **Chemical modification of DNA**

An enzyme, DNA methyltransferases (DNMTs) catalyze the DNA modifications. DNMTs usually transfer the methyl group from the S-adenyl methionine (SAM) to the cytosine residues to form the 5-methyl cytosine (5mC). Cytosine methylation usually occurs at the CpG site and then 5mC demethylated the thymine (Bird, 1980). These sites are found on the gene promoters regions, which are highly conserved and have high density of CpG sites (>50%). In general, these sites usually interfere with the transcription binding factors and repress the methyl binding domains of proteins (Bird et al., 1980; Nan et al., 1993).

In mammals, three different types of DNMTs exist: DNMT1 is the maintenance DNMT, as it binds to hemi-methylated sites and prevents demethylation during the DNA synthesis. DNMT3a and DNMT3b are the de novo DNMTs (Okanno et al., 1999). As a fact, DNMTs are abundantly expressed in the brain not only in the neurodevelopmental stage but also in the postmitotic neurons, which explains their role beyond the DNA methylation (Feng et al., 2005). The DNA methylation is a static epigenetic process that can only be affected by the demethylation during the cell division. So, the DNA methylation should be regulated. Ten-eleven translocations (TET) enzymes usually oxidise the 5mC. In the next step, it is deminated by the AID/ApoBec enzymes, which oxidise the TET enzymes. In the end, the oxidized product is removed by BER (Ito et al., 2011).
Many studies show that DNA methylation is related to intellectual by involving the genes. When considering the contextual fear conditioning in the rodent model to study memory; during memory formation, DNMTs are elevated in hippocampus, resulting in increased DNA methylation at the promoter of the memory suppressor gene PP1, and decreased methylation at the promoter of the synaptic plasticity gene RELN throughout memory consolidation (Miller and Swett, 2007). This also happens with the BDNF gene, in which DNA methylation occurs in the learning task, which results in increased BDNF exon I and IV in the fear memory consolidation (Lubin et al., 2008). The DNA methylation changes in the brain are transient and revert in 24 hours. This suggests that DNA methylation have significant involvement in the formation and consolidation of memories in the hippocampus (Figure 2).

Additionally, the brain exhibits elevated amounts of two additional categories of methylation: non-CpG methylation (mCH, where H represents adenine A, cytosine C, or thymine T) and hydroxymethylation (5hmC), both of which are involved in neuronal modifications (Varley et al., 2013; Song et al., 2011). mCH is not present in the fetal cortex but accumulates during postnatal development, leading to DNA methylation and gene repression in neurodevelopment. From this point, DNMT3a plays an important role in the neurons during development. Higher level of mCH in the glial cells causes the suppression of neuron-specific gene and methylated at the level of CH in the glial cells (Lister et al., 2013). Overexpression of TET1 causes disrupts the formation of contextual fear memories. (Kass et al., 2013), while the TET1 downregulation leads to deficiencies in synaptic plasticity and memory excitation (Rudenko et al., 2013).

Numerous researchers reported the function of DNA methylation in the hippocampus during memory formation and consolidation but have not explored the long-term storage of memories. It has been established that a burst of waves, known as sharp waves, promotes plasticity, facilitating the transfer of memories from the hippocampus to the neocortex (Wiltgen et al., 2004). These waves result in the epigenetic storing of learning in the cortical cells by DNA methylation and resistance to erasing the DNMT1 self-perpetuating mechanism, which usually methylated the hemi-methylated and unmethylated stands of DNA (Heyward and Sweatt, 2015). The CaN (calcineurin) gene is involved in the maintenance of memories, as delayed to persistent DNA methylation occurs in cortical neurons for 1 to over 30 days, respectively, causing contextual fear memory to transition from transient to remote (Miller et al., 2010).

2. Histone modification

The primary constituents of chromatin are histones, which can be categorized into four major types: H4, H2A, H3, and H2B. These histones correlated tightly with DNA to form a nucleosome. H1 controls the folding of the nucleosome, while posttranslational modifications (PTMs) govern chromatin compaction by modifying the protruding end of the histone tail (Bannister and Kouzarides et al., 2011). Several PTMs act on the tail of histone such as acetylation, methylation, phosphorylation, SUMOylation and ADP-ribosylation (Shin et al., 2015).

Histone acetylation usually causes a positive effect on chromatin folding by neutralizing acetyl group from the residues of lysine (K) and arginine (R), thus reducing the electrostatic interactions in the DNA nucleosome. These epigenetic writers are known as histone acetyltransferases (HATs), and the erasers known as histone deacetylases (HDACs) (Lopez and Barco, 2014). This histone acetylation causes memory regulation by the ERK/MAP pathway regulation in the cortex by lysine acetylation (Levenson et al., 2004). Many types of research revealed the HDACs inhibitor (HDADi) improves the cognitive impairment and increase memory and learning (Lopez and Barco, 2014). These modification causes the transcription and prepares the cells to initiate the gene regulation on signals (Lopez-Atlasy et al., 2013). CREB is a specific transcriptional factor that coactivates the CBP through HAT domain, increases the acetylation process at gene level, and helps in memory integration (Korzus et al., 2004)(Figure 2).

Many HDAC isoforms regulate the adult form, specifically at the histone acetylation level. For example, HDAC5 causes the hypersensitive response to chronic drug abuse (Tsankova et al., 2006); HDAC2 causes the deregulation in memory formation and synaptic plasticity (Guan et al., 2009), and HDAC3 inhibits long-term memory formation (McQuown et al., 2011). SIRT1 impairs the hippocampal formation of memory by decreasing the dendritic branching and spines, which is the special structure in learning (Michan et al., 2010). HDCA1 requires the deacetylation of H3K9 for the fear extinction learning (Bahari-Javan et al., 2012) and HDAC4 requires memory formation and synaptic plasticity (Kim et al., 2012).

The process of histone phosphorylation is closely linked to histone acetylation. Specifically, the phosphorylation of histone H3 at the serine (S) 10 site (H3S10P) occurs alongside the acetylation of histone H3K9. This biochemical event plays a critical role in forming spatial memory and activating many genes (such as c-Fos, Erg-1, and Arc) by the ERK/MAPK pathway (Carter et al., 2015).

The histone acetylation results in transcriptional regulation, while the methylation of histone effects mostly depends upon the docking protein complexes.
For instance, the H3K4 methylation and monomethylation of H3K9 cause transcriptional activation, while H3K9me2 and H3K9ma3 cause transcriptional knockdown. Histone methylation occurs either at lysine (K) or arginine (R) is mostly carried out by the SET of proteins domain known as histone methyl transferase (HMTs). HMTs are regulated by the histone demethylases (HDMs), such as LSD1 for H3K4me and H3K4me2 and JMJD1a for H3K9me and H3K9me2 (Lubin et al., 2011). Recent study in which mice deficit with Mll, a H3K4 methyltransferase, shows defects in fear memory formation (Gupta et al., 2010). GLP/G9a, an H3K9me2 methyltransferase, plays an important role in cognition and switching chromatin signals (Benevento et al., 2015), acting during development and modulating the gene expression by recruiting the enzymes. This complex helps in memory consolidation from hippocampus to cortex (Gupta et al., 2012). GLP/G9a is also important in developing the behaviour because its deficiency cause the defects in learning, memory and motivation (Schaefer et al., 2009).

### 3. Chromatin remodeling

Nucleosome remodeling complexes (NRCs) use ATP-dependent mechanisms to change the position of nucleosomes by enhancing nucleosome sliding, expulsion, and exchange of histone variants. Studies have shown that the neuron-specific Brg1/hBrm associated factor (nBAF) complex, which belongs to the SWI/SNF family, is involved in activating gene expression during both development and cognition. Upregulation of BAF45b and BAF45c subunits and BAF53a and BAF53b is essential in postmitotic neurons (Figure 2) and control the BRG1’s ATPase activity (Olave et al., 2012). The mice deficit with BAF53b showed large impairments in long-term memory consolidation (Vogel-Ciernia et al., 2013).

### 4. Noncoding RNAs (ncRNAs)

ncRNAs are part of the transcript that are not translated to proteins. It has two main categories: small RNAs and long noncoding RNAs (lncRNAs). The first comprehends the micro RNA (miRNA), which inhibits the gene expression at the target and interacts with PIWI interacting RNAs (piRNAs) and suppresses RNA mediated DNA methylation. The lncRNAs role is not well known but it regulates the gene expression by guiding and scaffolding RNAs and targeting the genomic locations (Cao et al., 2006). TUNA, RMST, and DALI regulate neuronal differentiation, which guide transcription factors, chromatin remodelling, and DNMTs to crucial locations (Chalei et al., 2014; Kerioglu et al., 2013). In many cases, methyl-binding proteins bring in HDACs, which work together through cytosine methylation and histone deacetylation to silence gene transcription (Vaisiere et al., 2008). By comparing these mechanisms, it can be said that gene expressions controlled brain activity by controlling the DNA methylation, histone acetylation and chromatin remodelling. (Figure 2)

![Figure 2](Image)

**Figure 2** | Epigenetic mechanisms in the intellectual disability; (1) chemical modification results in the methylation of DNA, (2) histone modifications causes the deacetylation and demethylation of the histone molecules, (3) in chromatin remodeling the BAF decreased results in ID and (4) noncoding RNAs decreased the RNA based DNA methylation. DMNT (DNA methyltransferases); HDAC (Histone deacetylase); HAT (Histone acetyltransferase); BAF(Brg1/hBrm associated factor); NRC (nucleosome remodeling complexes); miRNA (micro RNA); piRNA (PIWI RNA).
Treatment of ID
ID is now considered a neurodevelopmental disorder rather than just focusing on the intellectual level. A patient may adapt to existing environment if the positive reinforcements are given to them continuously. As ID cannot be cured completely, behavior is normalized according to society.

1. Environment enrichment
In this review, previously, it is pointed out that environment has a strong influence on epigenetic modifications. The microenvironment affects or interrupts the genome as any stage of development in any area of brain. The monzygotic pairs could show this effect, which are genetically similar but phenotypically changed if they drifted apart (Castillo-Fernandez et al., 2014). Environment enrichment (EE) is mostly used in rodent models to enhance learning and memory. For example, keeping the lab mice in EE with large cages and many toys to develop their sensory, cognitive and motor skills. The results showed that mice living in EE had improved learning and memory (Grill et al., 2009), and delayed deficits in neurological disorders mouse model (Nithianantharajah and Hannan, 2006). EE did not interfere with the genome but only improve the dendritic branching and spines as shown in Down’s syndrome model (Dierssen et al., 2003). In ID, the EE may cause some modification in the epigenetic mechanisms, as the EE only lasts for 3-4 weeks while behavioural changes are lifetime (Shin et al., 2013). Four weeks training in the EE conditions to rescue the contextual fear conditioning and water maze assays, there is an increased histone acetylation residues (Fischer et al., 2007). Understanding the complete mechanism to cure ID, a new class of therapeutics was developed known as enviro mimetics. Enviromimetics mimics the EE beneficial effects on learning (Nithianantharajah and Hannan, 2006). Many research using EE paves the way for the nonpharmacological treatment of ID.

2. Epigenetic drugs in ID
To understand ID and its treatment, a thorough gene profile was developed to know the key genes causing the impairments (Schaefer et al., 2015). A most promising way to last the transcriptional changes is by using cancer research (Dawson and Kouzarides, 2012). Epigenetic changes are reversible so alleviating some gene expressions will help control the ID. FDA already approves some drugs, two DNMT inhibitors (5-azacytidine and decitabine) and two HDAC inhibitors (Nebbioso et al., 2012). Also, the valproic acid, already utilized against the epilepsy and bipolar defects. It revealed the HDAC inhibition, anticholinergic action, and the first epiregul in used in neurological disorders (Papi et al., 2010). But in using these types of drugs caused the genome-wide and non-chromatin effect as they may interfere with the nonhistone proteins. So, much research are conducted to find the specific drugs that only target the particular gene (de Groote et al., 2012).

Conflict of interest
The authors declared absence of conflict of interest.

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